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1201 Constitution Ave., NW  
EPA East Room 6428  
Washington, DC 20004  
Attention: 8(e) Coordinator



**RE: Notification of Substantial Risk**



Dear Sir or Madam:

In accordance with Section 8(e) of the Toxic Substances Control Act (TSCA), Rhodia Inc. (Rhodia) is submitting the following information:

**"*In vivo* COMET ASSAY IN THE RAT STUDY PERFORMED ON STOMACH and DUODENUM with the compound CATECHOL (Two treatments, one sampling time)"**

In this study, the genotoxic potential of catechol (CAS# 120-80-9) was investigated in the *in vivo* comet assay performed under alkaline conditions, i.e. pH > 13 (Alkaline Single Cell Gel Electrophoresis) in the OFA Sprague Dawley male rat, stomach and duodenum, after two treatments by oral route at 3 dose levels (the maximum tolerated dose, MTD, 50% and 25% MTD), followed by one expression time of 3 to 6 hours after the last treatment.

In this assay, rats are treated two times at a 24-hour interval with the test compound at different dose levels. Three to six hours after the second treatment, the rats are killed and cells from the selected target organs are isolated. After isolation, single cells are embedded in agarose on microscope slides and successively submitted to lysis, unwinding and electrophoresis in alkaline conditions. After neutralization, slides are dried and stained with a fluorescent dye before analysis and scoring. The method used for quantifying DNA migration involves a computerized image analysis system in order to collect comet data; then, software calculates the metrics for DNA migration per the Olive Tail Moment (OTM), corresponding to the product of the tail length and the percentage of tail DNA.

In the initial study to determine the MTD, two groups of 4 male rats were dosed orally twice at 800 and 400 mg/kg/day. In the 800 mg/kg/day dose, very strong clonic convulsions occurred in all four male rats, 15 min to 30 min after the first treatment. For ethical reasons, the animals were euthanized and no second treatment was performed. The dose level of 400 mg/kg/day induced no death or clinical signs in the four male rats after the 1st or the 2nd treatment.

To determine if 400 mg/kg/day was the MTD, another group of 4 rats were treated at 500 mg/kg/day. The first treatment at the dose level of 500 mg/kg/day induced strong clonic convulsions in the four male rats, 15 min to 30 min after the first treatment. Three animals out of 4 died and for ethical reasons, the 4th animal was euthanized and no second treatment was performed. 400 mg/kg/day was confirmed as the MTD.

In the comet assay, five (5) male Sprague Dawley rats were treated orally with catechol at levels of 100, 200 and 400 mg/kg/day. No statistically significant increase in the OTM medians was observed in rat stomach cells treated with catechol at levels up to 400 mg/kg/day. The median OTM for 600 cells was 0.81, 0.35 and 1.13 at 400, 200 and 100 mg/kg/day, respectively, vs. 2.26 in the negative control group.

Under these experimental conditions, catechol induced no statistically significant increases in DNA strand breaks at non-lethal dose on rat stomach cells after oral administration.

Statistically significant increases in the OTM medians were observed in duodenum cells from rats, treated with the doses of 200 and 100 mg/kg/day of catechol. The median OTM for 600 cells (from the 4 animals analyzed per group) was 3.38 and 4.64 at doses of 200 and 100 mg/kg/day, respectively, vs. 1.48 in the negative control group. At these two dose-levels of 200 and 100 mg/kg/day, two animals out of the four treated, presented particularly strong increases in the median OTM, with values up to 6.07 and 4.21 at 200 mg/kg/day and 9.73 and 7.29 at 100 mg/kg/day. However, the dose of 400 mg/kg/day did not induce a statistically significant increase in the median OTM, with a value of 1.28. This value was below that of the OTM median for the control group. In fact the results showed a statistically significant increase in the median OTM, but with an inverse dose-effect relation, and a bell-shaped curve response. The test item was thus considered by the laboratory to be genotoxic to the rat duodenum cells.

Also in the comet assay, the laboratory reported that very strong clonic convulsions were observed 5 minutes after oral administration of catechol at the dose of 400 mg/kg/day, leading to one death between 30 minutes and 2 hours after the 1st treatment. Furthermore, the 4 animals were trembling after the 2nd treatment at 400 mg/kg/day. No clinical signs were reported in the animals treated with doses of 200 and 100 mg/kg/day.

Rhodia does not believe that the subject substance presents an unreasonable risk to workers, the public, or the environment when catechol is properly manufactured and used for its intended applications, but Rhodia believes that the submitted information may meet EPA's reporting criteria for TSCA Section 8(e).

This study was communicated to Rhodia Inc. on January 25, 2012.

Rhodia asserts that none of the information contained within this notice constitutes confidential business information (CBI) under TSCA.

Should you have any questions, or require further information, please do not hesitate to contact me at (215) 369-9734. Thank you.

Very truly yours,  
RHODIA INC.



Judith L. Kranetz  
Director, Regulatory Compliance & Product Stewardship

JLK/  
Atts

Ref: 12-009L 8(e).doc  
Via Federal Express

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Professeur Daniel MARZIN  
Tél. 33 (0)3 20 87 79 75  
Fax 33 (0)3 20 87 73 10  
e-mail : Daniel.Marzin@pasteur-lille.fr

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## FINAL STUDY REPORT CONFIDENTIAL

### STUDY TITLE

*In vivo* COMET ASSAY IN THE RAT

STUDY PERFORMED ON STOMACH and DUODENUM with the compound  
CATECHOL

(Two treatments, one sampling time)

### STUDY DIRECTOR

Dr. Fabrice NESSLANY

INSTITUT PASTEUR DE LILLE - Genetic Toxicology Laboratory  
1, rue du Professeur Calmette - BP. 245  
59019 LILLE CEDEX

### FINAL STUDY REPORT DATE

December 2<sup>nd</sup> 2008

### STUDY NUMBER

FSR-IPL 070402 / CATECHOL / RHODIA  
SGS MULTILAB phase number: BPL07-0029

### STUDY PERFORMED BY INSTITUT PASTEUR DE LILLE

1, rue du Professeur Calmette - BP. 245  
59019 LILLE CEDEX

### TEST SITES

SGS MULTILAB

Technopôle du Mardillet  
65, Rue Ettore Bugatti  
BP 90014

76801 Saint Etienne du Rouvray cedex

### PRINCIPAL INVESTIGATORS

Mr. Gregory Boullie

### SPONSOR

RHODIA

190, avenue Thiers  
69457 LYON cedex 06

### SPONSOR REPRESENTATIVE

Mr. Cyrille BOCQUILLOD

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## STUDY INFORMATION

**TITLE OF THE STUDY** : *In vivo* COMET ASSAY IN THE RAT STUDY PERFORMED ON STOMACH and DUODENUM (Two treatments, one sampling time)  
**SPONSOR** : RHODIA  
**TEST ITEM** : CATECHOL

### I. TESTING FACILITY INFORMATION:

**Test facility** : Institut Pasteur de Lille  
**Test facility address** : Genetic Toxicology Laboratory  
1, rue du Professeur Calmette - B.P. 245  
59019 LILLE CEDEX France

**Study director** : Dr. Fabrice NESSLANY  
**Deputy Study director** : Dr. Sophie SIMAR  
**Lead quality assurance** : Mrs. B. GOREZ  
**Test facility management** : Professor D. MARZIN  
Head of Toxicology Department

### II. SPONSOR INFORMATION:

**Sponsor** : RHODIA  
**Sponsor's address** : 190, avenue Thiers  
69457 LYON cedex 06  
**Sponsor representative** : Mr. Cyrille BOCQUILLOD

### III. ANALYTICAL TEST SITE INFORMATION :

#### 1. ANALYTICAL TEST SITE FOR BIONALYSIS OF DOSING FORMULATIONS :

**Analytical Test site address** : Technopôle du Madrillet  
65, Rue Ettore Bugatti  
BP 90014  
76801 Saint Etienne du Rouvray

**Study Phase Number** : BPL07-0029 (cf Amendment No. 3, Appendix No. 20)  
**Report Issued** : January 14<sup>th</sup>, 2008

**Principal investigator** : Mr. BOUILLIS Gregory  
Email: [gregory.bouillis@sgs.com](mailto:gregory.bouillis@sgs.com)  
Tel: +33 (0) 02 35 07 91 87

**Test site quality assurance** : Ms. SAPETA Corinne  
Email: [corinne.sapeta@sgs.com](mailto:corinne.sapeta@sgs.com)  
Tel: +33 (0) 2 35 07 91 85

**Test site manager** : Mr. GERVAISE Yvon  
Email: [yvon.gervaise@sgs.com](mailto:yvon.gervaise@sgs.com)  
Tel: +33 (0)2 35 07 91 80

#### 2. ANALYTICAL TEST SITE FOR BIONALYSIS OF PLASMA :

**Not performed**

## GOOD LABORATORY PRACTICE COMPLIANCE STATEMENT AND REPORT AUTHENTICATION

\*\*\*\*

The work described in this report was performed according to the agreed study plan and with the Standard Operating Procedures (SOP) of the testing facility, unless otherwise stated, and was conducted in accordance with:

- OECD Principles of Good Laboratory Practice (as revised in 1997), ENV/MC/CHEM(98)17;
- GLP Decree No. 98.1312 (Official Journal of 31<sup>st</sup> December 1998);
- GLP departmental order 14/3/2000 (Official Journal of 23<sup>rd</sup> March 2000);
- GLP departmental order 28/1/2005 (Official Journal of 20<sup>th</sup> February 2005);
- Application of the OECD Principles of GLP to the Organisation and Management of Multi-Site Studies, No. 13 Consensus Document of the Working Group on Good Laboratory Practice, ENV/JM/MONO(2002)9;
- EC Commission Directive 2004/10/EC of 11<sup>th</sup> February 2004 (Official Journal No. L050).

I consider the data generated and reported to be valid and I declare that this report is a true and accurate record of the results obtained.

As described on page 21 of the study plan FSP-IPL 070402, the sponsor certifies that the test item to be tested provided by RHODIA is identical to the test item described in the study plan and in the Analytical certificate.

Concerning the information about the test compound, data about its stability in the vehicle were available; however, the Catechol stability study was not performed under GLP status and did not cover the actual period of preservation (i.e. period between the preparation/collection process and the dosage). This constitutes a deviation to the recommendations of the Good Laboratory Practice (OECD 1997; §6.2, Characterization). Nevertheless, dosages showed that the differences between the nominal and the actual concentrations of the test item in the administered dosage forms were in an acceptable range of  $\pm 5\%$  demonstrating an acceptable stability of Catechol in the vehicle used under the conditions of preservation. Therefore, this deviation was considered as a minor deviation, which has no impact on the quality and/or the integrity of the current study.

The study was performed at the Toxicology Department of Institut Pasteur de Lille.

Submitted by:

Study director

Dr. Fabrice NESSLANY\*

01/12/2008

Date

  
Signature

Authorization of experimentation on animals \* No. 59-35068

Agreement of the establishment for realizing experiments on living vertebrate animals No. A59-35009

**STUDY** : *In vivo* COMET ASSAY IN THE RAT STUDY PERFORMED ON STOMACH  
and DUODENUM (Two treatments, one sampling time)

**TEST ITEM** : CATECHOL

**SPONSOR** : RHODIA

**This report was reviewed and approved by:**

Test facility management      **Professor D. MARZIN \***  
Head of Toxicology Department

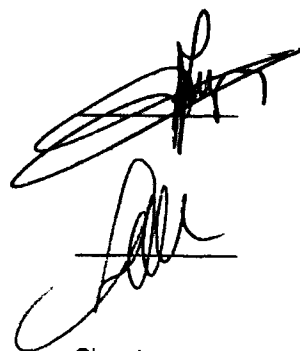
27/11/08

Deputy Study director      **Dr. Sophie SIMAR\*\***  
Assistant

21.12.07

Date

Signatures



Authorization of experimentation on animals No. \* 59-35001, No. \*\* 59-350156

Agreement of the establishment for realizing experiments on living vertebrate animals No. A59-35009

**QUALITY ASSURANCE STATEMENT**

\*\*\*\*

**TITLE OF THE STUDY** : *In vivo* COMET ASSAY IN THE RAT STUDY PERFORMED ON STOMACH and DUODENUM (Two treatments, one sampling time)

**TEST ITEM** : CATECHOL

**SPONSOR** : RHODIA

**STUDY LOCATION** : INSTITUT PASTEUR DE LILLE  
Genetic Toxicology Laboratory  
1, rue du Professeur Calmette - B.P. 245  
59019 LILLE CEDEX

This study was inspected by the Quality Assurance Unit, employing methods detailed in Standard Operating Procedures used at the Toxicology Department of Institut Pasteur de Lille. The analytical phases of the study (control of concentration in dosing formulations) were audited by **SGS MULTILAB**. These data are presented in the final report. The data presented in the report accurately reflect data collected during the conduct of the study. Any data supplied by or under the responsibility of the Sponsor were not subjected to review. Dates of inspection, phases inspected, and reporting dates are as follows:

	Inspection of procedures on this study			Inspection of procedures associated with this type of study		
	Inspection/ Audit	Study director report	Test facility Management report	Inspection/ Audit	Study director report	Test facility Management report
Receipt-acclimatization of animals	29/05/07	29/05/07	01/06/07			
Treatment of animals	25/09/07	25/09/07	03/10/07			
Toxicity	29/05/07	29/05/07	01/06/07			
Isolation of stomach cells				27/06/07	27/06/07	09/07/07
Isolation of duodenum cells				27/06/07	27/06/07	09/07/07
Comet assay	27/09/07	01/10/07	03/10/07			
Preparation of treatment solutions	25/09/07	25/09/07	03/10/07			
Reading of slides				26/07/07	26/07/07	20/08/07

	Inspection/Audit – Q.A. Report
Study Plan No. FSP-IPL 070402 - accepted by the study director on 28/05/07 - accepted by the sponsor representative on 06/06/07	28/05/07
Amendment No. 1 - accepted by the study director on 30/08/07 - accepted by the sponsor representative on 08/09/07	29/08/07
Amendment No. 2 - accepted by the study director on 28/08/08 - accepted by the sponsor representative on 3/09/08	20/08/08
Amendment No. 3 - accepted by the study director on 2/09/08 - accepted by the sponsor representative on 11/09/08	2/09/08
Amendment No. 4 - accepted by the study director on 10/10/08 - accepted by the sponsor representative on 15/10/08	10/10/08
Draft report	31/10/07
Final report	27/11/08

Quality Assurance Unit

  
Mrs Brigitte GOREZ

## ARCHIVE STATEMENT

The following study materials are retained in the archives of the Toxicology Laboratory of the Institut Pasteur de Lille (1, rue du Pr Calmette – 59019 Lille – France) for at least 10 years after the end of the study:

- Study plan and possible amendments,
- Raw data or authenticated copies thereof,
- Correspondence,
- Final report and possible amendments.

According to OECD Guideline Number 7 (as revised in 1997) point II 6.2.6 relative to the application of the Good Laboratory Practice Principles to short-term studies, at the sponsor's request and as mentioned in the Study Plan FSP-IPL 070402, the test article is destroyed at the end of the study.

In addition, raw data not specific to the study, including but not limited to certificates of analysis for food, water and sawdust and records of environmental data and equipments calibration are also archived at Institut Pasteur de Lille for at least 20 years.

Documents referring to the GLP study and study phase at the test site **SGS MULTILAB** (copy of study plan and subsequent amendments, satellite study design, final satellite report and raw data, etc.), are archived at the test site for 10 years. On completion of this period, with the approbation of the Sponsor, all archived documents referring to the Study Phase are destroyed or returned to the Sponsor.

***In vivo* COMET ASSAY IN THE RAT STUDY PERFORMED ON THE ON STOMACH and DUODENUM  
(Two treatments, one sampling time)**

**SUMMARY**

**SPONSOR** : RHODIA  
**TEST ITEM** : CATECHOL  
**BATCH NUMBER** : FPC0619301  
**STUDY LOCATION** : INSTITUT PASTEUR DE LILLE  
Genetic Toxicology Laboratory  
1, rue du Professeur Calmette - B.P. 245  
59019 LILLE CEDEX

**THIS STUDY WAS CARRIED OUT IN COMPLIANCE WITH GOOD LABORATORY PRACTICE  
REGULATIONS**

**METHOD**

Animals (species, sex, strain) : OFA Sprague Dawley male rats  
Number of animals per group : 4  
Form administered : solution  
Vehicle : distilled water  
Route : oral  
Dose volume : 10 mL/kg

Doses tested in the preliminary toxicity test : 800 – 500 – 400 mg/kg/ day (x 2)  
  
Maximum tolerated dose : 400 mg/kg/ day (x 2)  
Organs studied : stomach and duodenum  
Treatment schedule : two treatments, one sampling time  
Number of expression times : 1 at 3 to 6 hours after the last treatment

Doses used in the comet assay : **400 – 200 – 100 mg/kg/ day (x 2)**

*(analyzed doses appear in bold)*

Reference substances : dimethylhydrazine, 20 mg/kg (x1) for duodenum  
N-Methyl N'-nitro-N-nitrosoguanidine (MNNG), 20 mg/kg (x1) for stomach

Number of cells observed per animal : 150  
Number of cells observed per dose : 600  
(450 for the positive control)

**RESULTS****TOXICITY ASSAY**

DOSES in mg/kg/day (x2)	DOSING VOLUME	NUMBER OF ANIMALS	% MORTALITY 24 HOURS AFTER FIRST TREATMENT	% MORTALITY 24 HOURS AFTER SECOND TREATMENT
800*	10 mL/kg	4	100	-
400**		4	0	0

\*: 4 animals presented clonic convulsions after the 1<sup>st</sup> treatment. Animals were euthanased after 30 min.

\*\*: Neither mortality nor strong clinical signs were noted

DOSES in mg/kg/day (x2)	DOSING VOLUME	NUMBER OF ANIMALS	% MORTALITY 24 HOURS AFTER FIRST TREATMENT	% MORTALITY 24 HOURS AFTER SECOND TREATMENT
500*	10 mL/kg	4	75	-

\*: 3 animals with strong clonic convulsions and 3 dead after 25 min after the 1<sup>st</sup> treatment  
4<sup>th</sup> animal euthanased

The maximum tolerated dose of **CATECHOL** under these experimental conditions was set at 400 mg/kg/day (x2) by oral route in OFA Sprague Dawley male rats. The doses of 800 and 500 mg/kg elicited strong clinical signs, as described above.

**GENOTOXICITY ASSAY / STOMACH CELLS**

In vivo COMET ASSAY IN ISOLATED RAT STOMACH CELLS							
GROUP	COMPOUND	DOSES in mg/kg/day (x2)	OTM Median	F of Snedecor (homogeneity of variances)	NON PARAMETRIC statistical evaluation		Relative ratio of ghost cells
					p Kruskal-Wallis	p Mann-Whitney	
Solvent control	Distilled water	0	2.26	p<0.0001	p<0.0001	-	-
TREATED	Catéchol	400	0.81			p<0.0001	0.54
		200	0.35			p<0.0001	0.59
		100	1.13			p<0.0001	0.96
Positive control	MNNG	20 mg/kg/day (x1)	5.37	-	-	p<0.0001	0.95

No statistically significant increase in the OTM medians was observed in rat stomach cells treated with the three doses of **Catéchol**, i.e. 400 – 200 and 100 mg/kg/day (x2). Under these conditions, **Catéchol** was not considered as a DNA strand breaks and/or alkali-labile sites inducer on stomach cells.

**GENOTOXICITY ASSAY / DUODENUM CELLS**

<b>in vivo COMET ASSAY IN ISOLATED RAT DUODENUM CELLS</b>							
GROUP	COMPOUND	DOSES in mg/kg/day (x2)	OTM Median	F of Snedecor (homogeneity of variances)	NON PARAMETRIC statistical evaluation		Relative ratio of ghost cells
					p Kruskal- Wallis	p Mann-Whitney	
Solvent control	Distilled water	0	1.48	p<0.0001	p<0.0001	-	-
TREATED	Catéchol	400	1.28			N.S.	0.79
		200	3.38			p<0.0001	0.94
		100	4.64			p<0.0001	1.10
Positive control	Dimethylhydr azine	20 mg/kg/day (x1)	8.94	-	-	p<0.0001	0.87

Statistically significant increases in the OTM medians were observed in rat duodenum cells treated with the doses of 200 and 100 mg/kg/day (x2) of **Catéchol**. A clear inverse dose-effect relationship was noted. In return, the dose of 400 mg/kg/day (x2) did not induce any statistically significant increase in the median OTM.

It is noteworthy that the highest median OTM was observed at the lowest dose tested of 100 mg/kg/day (x2). The decrease in the values of median OTM at the two upper doses of 400 and 200 mg/kg/day (x2), compared to the dose of 100 mg/kg/day (x2), is most probably related to toxicity of the test item **Catéchol**, consistent with the clinical signs at the highest dose of 400 mg/kg/day (x2) described above. For the dose of 200 mg/kg/day (x2), the clinical signs did not indicate any toxic effect that could explain the decrease in the OTM value. In conclusion, the highest dose without genotoxic effect under the lowest dose tested of 100 mg/kg/day (x2), could not be determined in this study.

**CONCLUSION**

The test item CATECHOL (batch FPC0619301) provided by RHODIA was investigated by the means of the *in vivo* comet assay on stomach and duodenum, under alkaline conditions (SCGE) in the male OFA Sprague Dawley rats treated orally twice with 400, 200 and 100 mg/kg/day, with one sampling time 3 to 6 hours after the last treatment. Following the results of the toxicity assay, the maximum tolerated dose (MTD) determined was of 400 mg/kg/day. This dose was retained as the maximum dose to be tested, as well as two lower doses corresponding to MTD/2 and MTD/4. These two doses were not toxic, indeed, no clinical signs were observed.

Under these experimental conditions, CATECHOL induced no statistically significant increases in DNA strand breaks at non-lethal dose on rat *stomach* cells after oral administration. CATECHOL is hence devoid of genotoxic activity on the *stomach*.

In return, CATECHOL induced statistically significant increases in DNA strand breaks at non-lethal doses on rat *duodenum* cells after oral administration, with the highest increase of median OTM at the lowest dose tested of 100 mg/kg/day (x2). Furthermore, the very low cell density observed at the two highest doses tested during image analysis, indicates a probable cell lysis due to cytotoxicity and /or highly damaged cells with loss of information. Regarding the criteria described in paragraph 9, a test item is found to demonstrate genotoxic properties against the target organ if it results in a statistically significant increase in the OTM median compared with the negative control group and if the genotoxicity detected shows a dose-effect relationship. In fact the results showed a statistically significant increase in the median OTM, but with an inverse dose-effect relation, with a bell-shaped curve response. The test item Catechol was thus considered as genotoxic on rat duodenum cells.

It would be useful to implement a complementary assay under the same experimental conditions on duodenum cells only, but using doses lower than 100 mg/kg/day (x2), in order to determine if there is a high dose without genotoxic effect under the dose level of 100 mg/kg/day (x2). Under these conditions, CATECHOL was considered as a DNA strand breaks and/or alkali-labile sites inducer on *duodenum* cells.

A satisfactory agreement was observed between the actual and nominal concentrations of CATECHOL in treatment solutions used in the *in vivo* comet assay performed on stomach and duodenum. Indeed, the deviations from nominal concentrations were within an acceptable range of  $\pm 10\%$ .

***In vivo* COMET ASSAY IN THE RAT  
STUDY PERFORMED ON STOMACH and DUODENUM  
(two treatments, one sampling time)**

**A. GENERAL STUDY PLAN**

The single cell gel electrophoresis (SCGE) assay, also known as the "Comet assay", is a rapid, simple, visual and sensitive technique for measuring and analysing DNA breakage in mammalian cells (Östling and Johanson, 1984; Singh *et al.*, 1988; Olive *et al.*, 1990).

**1. PURPOSE OF THE STUDY**

The purpose of the *in vivo* Comet assay following the alkaline version (pH > 13) developed by Singh *et al.* (1988), is to identify those agents, which induce DNA damage such as single or double DNA strand breaks (SSB or DSB), alkali-labile sites, DNA-DNA / DNA-protein cross-linking and SSB associated with incomplete excision repair sites. The advantages of the Comet assay include its demonstrated sensitivity for detecting low levels of DNA damage.

The purpose of this study is to assess the genotoxic activity of the test compound in one or several target organs under these experimental conditions.

**2. PRINCIPLE**

Rats are treated two times at a 24-hour interval with the test compound at different dose levels. Three to six hours after the second treatment, the rats are killed and cells from the selected target organ(s) are isolated using specific enzymatic treatment schedules. After isolation, single cells are embedded in agarose on microscope slides and the obtained microgels are successively submitted to lysis, unwinding and electrophoresis in alkaline conditions and under dimmed light to prevent any additional DNA damage. After neutralization, slides are dried and could therefore be stained with a fluorescent dye (e.g. propidium iodide) before analysis and scoring. The method used for quantifying DNA migration involves a computerized image analysis system in order to collect comet data; then, the dedicated software allows indeed the calculation of metrics for DNA migration as the one introduced by Olive *et al.* (1990), *i.e.* the Olive Tail Moment (OTM), corresponding to the product of the tail length and the percentage of tail DNA. Although at present, there is no OECD guideline for this assay, this study plan is in agreement with recent international recommendations. Several workshop reports or reviews defined the optimal conditions to implement the comet assay in the state of the art (Tice *et al.*, 2000; Hartmann *et al.*, 2004; Burlinson *et al.*, 2007).

**3. CHOICE OF REACTIVE SYSTEM**

Male rats are commonly used in this test and are recommended in workshop reports or reviews.

**4. ANIMALS AND HUSBANDRY**

Young adult male OFA Sprague-Dawley rats (Charles River France origin, Saint-Germain-sur-l'Arbresle; FRANCE) weighing approximately 200 g and 5 to 10 weeks old, are used for the study. The period of acclimatization is at least 5 days. The animals receive a clinical examination in order to retain only the healthy ones.

At the start of the study, the weight variation of animals should be minimal and not exceed  $\pm 20$  % of the mean weight.

The animals are not fasted at the treatment time.

The animals are housed in polypropylene cages measuring 42.5 x 26.6 x 15 cm, covered by a stainless steel netted lid, in which they are placed in groups of 3 or 2 by random-distribution. The animals are identified by numbered ear rings.

The cages are placed in a ventilated cupboard slightly overpressurized relative to the animal room that is also ventilated.

The bedding consists of dust-free, sterilized wood shavings.

The feedstuff used is No. A04C10 irradiated rat/mouse feed from SAFE.

Drinking water softened, treated by osmosis and filtered on 0.2 µm membrane is provided ad libitum.

The temperature in the ventilated animal cupboard is  $22 \pm 3$  °C, and humidity is  $55 \pm 15$  %.

Ventilation renews the air 20 times per hour. A timer provides lighting 12 hours a day (8 a.m. - 8 p.m.) in all the animal rooms.

## 5. PRELIMINARY TOXICITY TEST AND CHOICE OF DOSES

This test is performed in order to determine the maximum tolerated dose (MTD) that is chosen as the highest dose in the *in vivo* Comet assay.

The maximum tolerated dose (MTD) is described as the highest dose which causes no mortality, but which may give rise to the appearance of weak signs of toxicity. However, if a substance causes excessive signs of toxicity (for example: lethargy) suggesting that the animal's metabolism may be disturbed, a lower dose, chosen according to the symptoms, is administered.

In an effort to reduce the number of laboratory animals required, the toxicity test is performed according to the improved experimental design recommended by Fielder et al. (1992), using a large series of doses chosen in accordance with available toxicological data.

In the preliminary toxicity assay, 4 male rats per dose are used. Following dosing, the animals are observed regularly for a period of at least 48 hours and any clinical signs and/or any mortalities are recorded. The results are given in the form of tables.

The highest dose used for the *in vivo* Comet assay is the MTD. The lower doses should be 50% to 25% of the highest dose (MTD/2 and MTD/4).

For non-toxic products, the maximum dose of 2 g/kg or the maximum dose that can be administered practically to the animals, whichever is lower, will be chosen as the test highest dose.

## 6. MATERIAL AND METHOD

### 6.1 Formulation of the test compound

Solid substances are dissolved or suspended in appropriate solvents or vehicles and then diluted with the same solvent or vehicle if necessary. In case of suspensions only, a suspension for each dose is prepared individually. Liquid substances are dosed directly or diluted prior to dosing. Preparations for treatment are performed just before use.

#### Dose levels

From the results of the preliminary toxicity test, two dose levels are chosen for each genotoxicity assay.

An additional and provisional low dose level group is also incorporated into the experimental design. It would be assessed for DNA fragmentation in the *in vivo* Comet assay in the case of excessively low cell yields or mortality occurring at the highest dose or in order to establish either a dose-effect relationship or to find a no genotoxic effect dose.

## 6.2 Dosing of animals

Healthy animals are randomly assigned to the control and treatment groups. Four animals are used in the negative and treated groups and three for the positive control groups. The test compound is administered using two treatments at a 24-hour interval by gavage with the standard dose volume of 10 mL/kg. More than the required minimum of 4 animals are treated at each experimental point (5) to allow for possible mortality or problems encountered during cell isolation step. Other routes of exposure may be acceptable when justified. In the current study, the oral route and administration by gavage is the most appropriate in order to characterise the genotoxic activity of **catechol** in the stomach and the forestomach and in particular to demonstrate whether or not catechol is a direct genotoxic.

Negative controls are animals treated with vehicle in the same condition as treated animals (same route and vehicle).

Positive control animals are usually treated by oral route using a single treatment.

## 6.3 Expression times (Sampling times)

One expression time between 3 to 6 hours after the second treatment is performed for the *in vivo* Comet assay. At the end of the expression time, animals are sacrificed and the cells of the target organs are isolated.

The repartition of treatment groups is summarized in the following Table:

Group	Treatment	Dosage	Number of animals used*
			3-6 hours after the 2 <sup>nd</sup> treatment
1	Vehicle		4 (5)
2	Test compound	Additional low dose** (MTD/4)	4 (5)
3	Test compound	mid dose (MTD/2)	4 (5)
4	Test compound	high dose (MTD)	4 (5)
5	Dimethylhydrazine (duodenum)	10 mg/kg	3 (4)
6	MNNG (stomach)	20 mg/kg	3 (4)

\* Number of animals used in the test: the numbers indicate the number of animals used for cell isolation and, in brackets, the number of animals actually treated for the test.

\*\* Group 2: an additional and provisional low dose level group which would only be assessed for the DNA fragmentation in the *in vivo* Comet assay in the event of unacceptably low cell yields or mortalities occurring in group 4, or in order to establish either a dose-effect relationship or to find a no genotoxic effect dose.

These positive controls have been chosen because they have as target organ the stomach (MNNG) and the duodenum (DMH) and are known as specific carcinogens in these organs.

## 6.4 Cell isolation(s)

The 5 animals of each group are assigned for cell isolation, but only 4 randomly animals are actually assessed for DNA fragmentation (the 5<sup>th</sup> animal could be assessed in the case of discrepant or equivocal results).

Individual animals are anaesthetized with pentobarbital (60 mg/kg) and maintained under deep anaesthesia to prevent any likelihood of recovery.

#### 6.4.1 Stomach

The abdominal surface of the animal is rinsed with 70% (v/v) ethanol and a 'V' shaped incision is made from the centre of the lower abdomen to the rib cage. The skin and muscles are removed to reveal the abdominal cavity. The stomach is removed, opened and rinsed with calcium- and magnesium-free phosphate buffer saline (PBS). The forestomach is discarded and the cells of gastric mucosa are isolated by enzymatic digestion following Burlinson *et al.* (1989) and Brault *et al.* (1999) as described hereafter:

The gastric mucosa is incubated in calcium- and magnesium-free Hank's balanced salt solution (HBSS) containing 50 U/mL protease at 37 °C for 30 minutes in the oven. After the first incubation period, the mucosa is then flushed with the incubation medium to remove cells. The cell suspensions are centrifuged at 350 g for 5 minutes. The cell pellets are resuspended in HBSS containing 0.25 % dispase II and the suspensions are incubated at 37 °C for 15 minutes in a hot-bath.

After the second incubation period, 0.5 mL of fetal calf serum is added and the cell suspensions are filtered through a 150 µm nylon filter. The cell suspensions are then centrifuged at 350 g for 5 minutes and the cells are resuspended in HBSS.

The proportion of viable cells is determined with the help of a Malassez haemocytometer using Trypan blue technique as described in 6.6 before preparing slides to be assessed for DNA fragmentation (see paragraph 6.7: Comet assay).

#### 6.4.2 Duodenum

The abdominal surface of the animal is rinsed with 70% (v/v) ethanol and a 'V' shaped incision is made from the centre of the lower abdomen to the rib cage. The skin and muscles are removed to reveal the abdominal cavity. The totality of the duodenum is removed and rinsed with calcium- and magnesium-free phosphate buffer saline (PBS). Cells of duodenum are isolated by enzymatic digestion following Evans *et al.* (1992) as described hereafter.

Firstly, a ligature is tightened at one end of each duodenum sample. Then, a mix of collagenase XI and dispase I (300 U/ml, 0.02 %) is directly injected into the sample of duodenum using a syringe and a second ligature is placed on the other end of the sample of duodenum. The sample of duodenum filled with the enzymatic mix is then incubated for 30 minutes at 37 °C in a hot-bath, in 10 mL of HBSS. After the incubation period, around 0.2 mL of fetal calf serum is added. The sample of duodenum is then opened and carefully scrapped in order to facilitate the cell dissociation. After that, the cell suspension is centrifuged 5 minutes at 150 g. The cell pellets are resuspended in HBSS.

The proportion of viable cells is determined with the help of a Malassez haemocytometer using Trypan blue technique as described in 6.6 before preparing slides to be assessed for DNA fragmentation (see paragraph 6.7: Comet assay).

### **6.5 Determination of the cytotoxicity of the compound**

Cytotoxicity is determined on a small sample of each isolated cell suspension following the Trypan blue vital dye exclusion technique.

In accordance with a recognized group of scientists, the decrease in the viability should not be more than 30 % when compared to the concurrent control (Tice *et al.*, 2000). Cell viability in the target tissue that is below 70 % of that in the control animals may thus be considered excessive.

Therefore, according to the data obtained from the cytotoxicity assessment, doses are actually selected for genotoxicity assessment (two dose levels are chosen for each structured organ).

At least  $1.2 \times 10^5$  viable cells are required for proceeding to slides preparation (4 slides with  $3 \times 10^4$  viable cells per slide) as described in 6.7.

## 6.6 Preparation of specific reagents for comet assay

### 6.6.1 Lysis stock solution (pH 10)

The composition of the lysis stock solution is the following:

- NaCl 2.5 mM
- EDTA 100 mM
- Trizma Base 10 mM
- NaOH 12 g/L

The final lysis solution contains 89 % of lysis stock solution, 10 % of DMSO and 1 % of Triton X-100.

### 6.6.2 Electrophoresis buffer

The final electrophoresis buffer contains 30 mL of NaOH 10 N solution, 5 mL of EDTA 200 mM (pH = 10) solution and 965 mL of distilled water.

### 6.6.3 Neutralization buffer

The neutralisation buffer contains Trizma Base 400 mM (pH = 7.5).

### 6.6.4 Staining stock solution

The staining stock solution contains 1 mg/ml of Propidium iodide in distilled water.

Just prior to use, the staining stock solution is  $1/10^{\text{th}}$  diluted in water to obtain the final staining solution.

## 6.7 Comet assay

The Comet assay is performed under alkaline conditions essentially following the procedure of Singh *et al.* (1988). At least three slides are prepared for each animal, with 4 animals per group, *i.e.* at least 12 slides per type of treatment (negative and positive control and two dose levels). Fifty cells per slide are randomly scored, *i.e.* 150 cells per animal.

The essential steps of comet assay are successively, layering of cells mixed with low melting point agarose (over coated glass microscope slides), lysis (to lyse the cell and nuclear membranes and other proteins), unwinding of DNA, electrophoresis, neutralization, staining and scoring.

### 6.7.1 Dried slides preparation (pre-layering)

Conventional slides are dipped in a 1.5 % normal melting point agarose in PBS while it is hot. After gently remove, underside of slides is wiped in order to remove excess agarose. The slides are then laid in a tray on a flat surface to dry.

### 6.7.2 Slide preparation

Before use, a volume of 85  $\mu\text{L}$  of 0.8% of Normal Agarose (NA) is added on microscope slide pre-layered with 1.5% of NA (as described above in 6.8.1) and cover with a glass coverslip. Slides are placed on a slide tray resting on the ice packs until the agarose layer hardens (3 to 5 minutes). Around  $3 \times 10^4$  cells of the different concentrations tested are mixed with 75  $\mu\text{L}$  of 0.5% of Low Melting Point Agarose (LMPA) kept at 37 °C and added on microscope slide after gentle slide off the coverslip. They are then covered with a new glass coverslip. Slides are placed on a slide tray on ice packs for 3 to 5 minutes.

### 6.7.3 Lysis

After the top layer of agarose has solidified, the glass coverslips are removed and the slides are immersed for at least 1 hour at + 4 °C in the dark in a lysing solution consisting of 2.5 M NaCl, 100 mM EDTA, 10 mM Tris, pH 10, to which 1% Triton X-100 and 10% DMSO are freshly added (pH adjusted to 10 with NaOH).

### 6.7.4 Unwinding, electrophoresis and staining

The slides are then removed and placed on a horizontal gel electrophoresis unit and the unit filled with freshly prepared alkaline buffer (1 mM EDTA and 300 mM NaOH, pH > 13) to around 0.25 cm above the slides. In order to avoid excessive variation across the groups during each electrophoretic run, for each animal only one of the quadruplicate slides is processed in each run (DNA – unwinding and electrophoresis). The cells are exposed to the alkali for 20 minutes to allow the DNA unwinding, and expression of single-strand breaks and alkali-labile sites. Next, electrophoresis is conducted for 20 minutes at 0–4°C by applying an electric current of 0.7 V / cm (25 V / 300 mA). All these steps are conducted sheltered from the daylight to prevent the occurrence of additional DNA damage. After electrophoresis at pH >13, the slides are neutralized twice for 5 minutes with 0.4 M tris (pH 7.5) and the DNA is exposed for 5 minutes to absolute ethanol in order to preserve all the comet assay slides [34]. Subsequently, the slides are airdried and then stored at room temperature until they are scored for DNA migration.

Just prior to scoring, the DNA is stained using Propidium Iodide (20 µg/mL distilled water; 30 µL/slide).

### 6.7.5 Image analysis

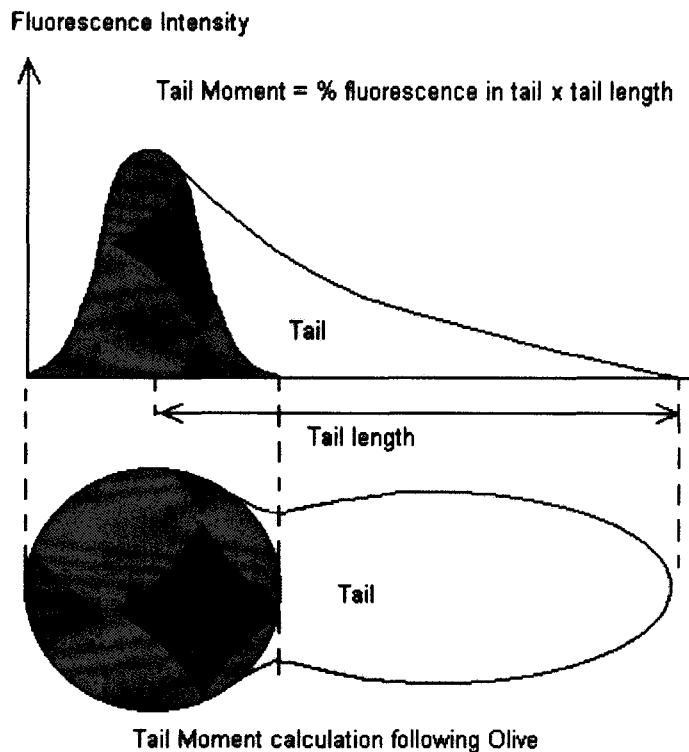
Slides are examined at 250 x magnification using a fluorescent microscope (Leica Microscopy and Scientific Instruments Group, Heerbrugg, Switzerland) equipped with an excitation filter of 515-560 nm and a barrier filter of 590 nm, connected through a gated CCD camera to Comet Image Analysis System, version 4.0 software (Kinetic Imaging Ltd, Liverpool, UK).

At least three slides are prepared for each animal, with 4 animals per group, *i.e.* at least 12 slides per type of treatment (negative and positive control and two dose levels). Fifty cells per slide are randomly scored, *i.e.* 150 cells per animal.

### 6.7.6 Tail parameters

Olive Tail Moment (OTM) preconised by Olive (1993) is used to evaluate DNA damage. The OTM, expressed in arbitrary units, is calculated by multiplying the percentage of DNA (fluorescence) in the tail by the length of the tail in µm (B. Hellman *et al.*, 1995; E. Rojas *et al.*, 1999). The tail length is measured between the edge of comet head and the end of the comet tail.

A major advantage of using the OTM as an index of DNA damage is that both the amount of damaged DNA and the distance of migration of the genetic material in the tail are represented by a single number (J. Ashby *et al.*, 1995).



## 7. EXPRESSION OF THE RESULTS AND STATISTICAL ANALYSIS

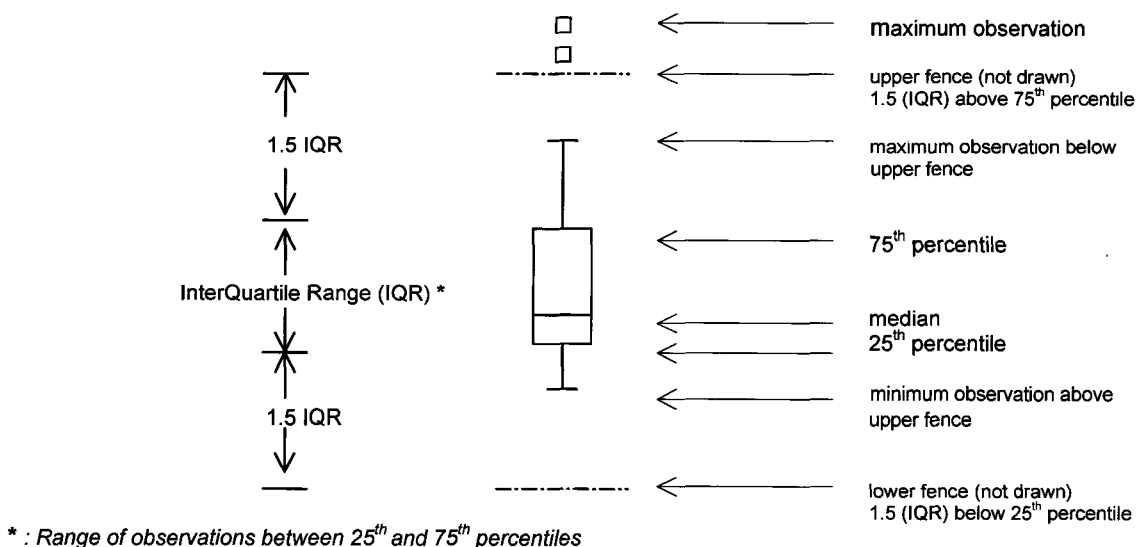
### 7.1 Expression of the results

□ At least three slides are prepared for each animal with 4 animals per group, *i.e.* at least 12 slides per type of treatment (negative and positive control and two dose levels). Fifty cells per slide are randomly scored, *i.e.* 150 cells per animal.

The results obtained in the different treatments are presented in tabular form giving the OTM median for at least 150 cells per animal.

In addition, each slide was also examined for presence of ghost cells (possible indicator of toxicity and or apoptosis). Ghost cells are excluded from image analysis data collection. However, determining their frequency might be useful for data interpretation. Therefore, the percentage of ghost cells is recorded for each slide per animal, per type of treatment and per organ. The ghost cells, also known as clouds or hedgehogs, are morphological indicative of highly damaged cells often associated with severe genotoxicity, necrosis and apoptosis. A ghost cells results from a total migration of the DNA from the nucleus into the comet tail, reducing the size of the head to a minimum.

- For each assay, a box plot on Olive Tail Moment over group is realized in order to show the distribution per slide per animal as described above:



- According to the 4th International Workshop on Genotoxicity Testing (Burlinson et al., 2007) as Tail Moment is used, Tail length and %Tail DNA data will be presented under tabular form.

## 7.2 Statistical analysis

In order to quantify the test item effects on DNA, the following statistical analysis strategy is applied, using the statistical software **Stat view**, version 5.

Before analyzing the OTM median of the treated groups, the absence of statistically significant differences between group variances is verified. The group variances are compared (OTM of total group without positive control) using the **F of Snedecor** (F- test) at the 0.05 significance level.

### 7.2.1 Homogeneity of variance : Statistical analysis using parametric tests

- When differences between group variances are not found to be significant, a parametric, one-way analysis of variance ANOVA is performed. Linear regression analysis is used to determine *dose-response relationships*.
- Pair-wise comparisons t-test are used to compare each of the doses tested with the vehicle control, to determine if a particular dose shows a difference with respect to vehicle control. Pair-wise comparisons t-test is also used to compare vehicle control and positive control to determine acceptable criteria of a valid test.

### 7.2.2 Non-homogeneity of variance: Statistical analysis using non-parametric tests

- When differences between group variances are found to be significant, the OTM frequencies and other tail parameters do not follow a gaussian distribution (E. Bauer et al., 1998). The non-parametric, one-way Kruskal-Wallis test is then performed. This method is based on the analysis of variance by ranks for testing equality of population medians among groups, in order to display a possible dose-response relationships.
- The non-parametric Mann-Whitney U-test is applied to compare each of the doses tested with the vehicle control in order to determine statistical significance of differences in group median values between each group versus the vehicle control. This test is also used to compare vehicle control and positive control to determine acceptable criteria of a valid test.

## 8. ACCEPTANCE CRITERIA FOR THE RESULTS

A study is accepted if both following criteria are fulfilled:

- In the solvent control group, the OTM median must be lower than 8.
- In the positive control groups, the OTM median must be statistically increased compared to the control group.

## 9. INTERPRETATION OF THE RESULTS

A test item is found to demonstrate genotoxic properties against the target organ if it results in a statistically significant increase in the OTM median compared with the negative control group and if the genotoxicity detected shows a dose-effect relationship.

However, statistically significant increases with values inside the limits of negative historical control data are considered as non-biologically relevant.

A test item is found to have no genotoxic effect on the target organ if it does not comply with any of the criteria listed above.

In case of significant increases in OTM median compared to vehicle control without a clear dose-relationship or no increase in any of the treated groups with evidence of a dose-response, the test item is considered as equivocal.

If neither situation occurs, the results are discussed case by case and another independent study may be implemented after modifying the dose range taking into account all available relevant data. Any complementary assay will be the subject of a new study plan.

The criteria are not absolute but do constitute an aid to decision, which will make it possible to reach a conclusion in most cases.

## 10. CONTROL OF CONCENTRATION IN DOSING FORMULATIONS

The sponsor chose to check the concentration of **CATECHOL** in dosing formulations.

In that case, this study is a multi-site study as defined in the consensus document No.13 of OECD: the Application of the OECD Principles of GLP to the Organization and Management of Multi-Site Studies.

The test site Quality Assurance audited this part of the study and sent a copy of the audits to the test facility management, the study director and the lead Quality Assurance.

Deviations from the study plan or Standard Operating Procedures (SOPs) related to the study should be documented at the test site, be acknowledged by the Principal Investigator and reported to and acknowledged by the Study Director in a timely manner. The study director will assess the impact of each event on the quality and/or the integrity of the study.

For each part of the multi-site study, a phase study report is issued and sent to the Study Director. It includes the results, a Principal Investigator statement of compliance and a test site quality assurance statement.

The corresponding results are inserted in the Final Report in Appendix No. 22 and they may be discussed in the conclusion.

### 10.1 Control of concentration in dosing formulations

The sponsor chooses to perform the check of the concentration of **CATECHOL** in dosing formulations.

Aliquots of **each dosing formulation** were sent to the laboratory in charge of analysis.  
For details, see paragraph C2 of the current report.

## 11. STUDY PLAN ADHERENCE

The current study was carried out in compliance with the Final Study Plan FSP-IPL 070402 and amendments. At Sponsor's request, the 3<sup>rd</sup> dose of 100 mg/kg/day (x2) was also analyzed.

Slides were not examined with the Comet Image Analysis System as stated page 13 of the Final Study Plan, but with a 200 x magnification, using a fluorescent microscope (Leica Microsystems - DM 2000, Heerbrugg, Switzerland), equipped with an excitation filter of 515-560 nm and a barrier filter of 590 nm, connected through a gated monochrome CCD IEEE1394 FireWire video camera (Allied Vision Technologies), to Comet Assay IV Image Analysis System, version 4.11 with Windows XP Pro Software (Perceptive Instruments Ltd, Suffolk, UK).

No other deviation from the Final Study Plan was observed.

**B. GENERAL INFORMATION AND SPECIFIC PROTOCOL**

**SPONSOR** : *In vivo* COMET ASSAY IN THE RAT STUDY PERFORMED ON STOMACH and DUODENUM (Two treatments, one sampling time)

**TEST ITEM** : CATECHOL

I.P.L. REGISTRATION NUMBER : 060719

BATCH NUMBER : FPC0619301

EXPIRY DATE : 14-07-2008

APPEARANCE : beige to brown flakes

QUANTITY SUPPLIED : approximately 200 g

PURITY : 99.7%

STORAGE : at room temperature, away from light and air (may discolour)

STABILITY IN STORAGE CONDITIONS : 14/07/2008

This test item, the characteristics of which are given in Appendix No. 13, was tested in accordance with the Final Study Plan, with the following exceptions or particularities:

The test item presents a purity of 99.7%, a purity correction was made.

Animals : rat: OFA Sprague Dawley  
sex: male only  
weight: 156 g to 192 g

Feedstuff No. A04C10 irradiated : SAFE, Batch 61124

Form administered : solution

Vehicle : distilled water

Stability in vehicle : stable at -18°C during 2 months

Route : oral route

Dose volume : 10 mL/kg

Maximum tolerated dose : 400 mg/kg/day (x2)

Organs studied : stomach and duodenum

Treatment schedule : treated and control groups: two treatments with a 24-hour interval  
positive control groups: one treatment

Number of expression times : 1: 3 to 6 hours after the last treatment

Doses used in the comet assay  
(analyzed doses appear in bold) : **400 – 200 – 100** mg/kg/day (x2)

Reference substances : STOMACH: N-Methyl N'-nitro-N-nitrosoguanidine (MNNG)  
(Aldrich, Batch 15427LO), oral route, 20 mg/kg (at 10 mL/kg)

DUODENUM: dimethylhydrazine (Fluka, Batch 419144/1 34800)  
oral route, 20 mg/kg (at 10 mL/kg)

Number of cells observed/animal : 150

Number of cells observed/dose : 600

450 for positive control

- In-life phase:

Experimental starting / completion date : 28/05/07 – 22/10/07

## **C. RESULTS**

The genotoxic potential of **CATECHOL (batch FPC0619301)** from **RHODIA** was investigated in the *in vivo* comet assay performed under alkaline conditions, *i.e.* pH > 13 (Alkaline Single Cell Gel Electrophoresis) in the OFA Sprague Dawley male rats, stomach and duodenum, after two treatments by oral route at 3 dose levels (the maximum tolerated dose, MTD, 50 and 25% MTD), followed by one expression time of 3 to 6 hours after the last treatment.

The current protocol is in agreement with recent international recommendations, several workshop reports or reviews which defined the optimal conditions to implement the comet assay in the state of the art (Tice et al., 2000; Hartmann et al., 2004; Burlinson et al. 2007).

### **1. PREPARATION OF DOSING FORMULATIONS**

In accordance with the Final Study Plan, the test **CATECHOL** was dissolved in distilled water up to a maximum concentration of 80 mg/mL (toxicity assay) or 40 mg/mL (genotoxicity assay) and administered at a dose volume of 10 mL/kg, giving final doses of 800 and 400 mg/kg, respectively. The different inferior dilutions were also performed with distilled water.

Regarding the positive reference substance, both MNNG and dimethylhydrazine were dissolved in distilled water and administered under a dose volume of 10 mL/kg by oral route.

### **2. CONTROL OF CONCENTRATION IN DOSING FORMULATIONS**

In agreement with the study plan FSP-IPL 070402, samples of **each dosing formulation (volume of 2 x 1 mL)** used in the main genotoxicity assay were stored frozen at  $-18 \pm 3^{\circ}\text{C}$ , prior to dispatching on dry ice at the end of the study to the Principal Investigator in charge of control of concentration in treatment solutions:

Name, surname : Mr. Gregory BOUILLIS  
Address : **SGS MULTILAB**  
Technopôle du Madrillet  
65, Rue Ettore Bugatti  
BP 90014  
76801 Saint Etienne du Rouvray

Results of **CATECHOL** concentrations in dosing formulations are presented in the final report, Appendix No. 22.

A satisfactory agreement was observed between the actual and nominal concentrations of **CATECHOL** in treatment solutions used in the *in vivo* comet assay performed on stomach and duodenum. Indeed, the deviations from nominal concentrations were within an acceptable range of  $\pm 10\%$ . Furthermore, solutions of **CATECHOL** can be considered as stable at  $-18^{\circ}\text{C}$ , during two months.

The second aliquots were kept in the same preserving conditions at Institut Pasteur de Lille. The back-up samples were not used and were thus destroyed at the finalization of the study report.

### 3. TOXICITY TEST

Results of the toxicity test by the oral route in OFA Sprague Dawley male rats (preliminary and confirmatory assays) are summarized in Table 1.

In this toxicity assay, two groups of 4 male rats were dosed orally twice at 800 and 400 mg/kg/day. The maximum tolerated dose of **CATECHOL** was set at 400 mg/kg/day (x2) by oral route in OFA Sprague Dawley male rats. Indeed, the dose of 800 mg/kg/day (x2) elicited strong clinical signs, as described below and at the dose of 500 mg/kg/day (x2), 3 animals out of 4 died 25 min after the first treatment. In return, the dose of 400 mg/kg/day (x2) induced no clinical signs.

#### **DOSE OF 400 MG/KG/DAY (X2)**

The dose level of 400 mg/kg/day (x2) induced no death or clinical signs in the four male rats after the 1<sup>st</sup> or the 2<sup>nd</sup> treatment.

#### **DOSE OF 800 MG/KG/DAY (X2)**

The first treatment at the high dose level of 800 mg/kg/day (x2) induced very strong clonic convulsions in the four male rats, 15 min to 30 min after the first treatment. For ethical reasons, the animals were euthanased and no second treatment was performed.

In order to confirm that the dose of 400 mg/kg/day (x2) is the actual maximum tolerated dose in OFA Sprague Dawley male rats, a 2<sup>nd</sup> toxicity assay with a third intermediary dose of 500 mg/kg/day (x2) was implemented.

#### **DOSE OF 500 MG/KG/DAY (X2)**

The first treatment at the dose level of 500 mg/kg/day (x2) induced strong clonic convulsions in the four male rats, 15 min to 30 min after the first treatment. Three animals out of 4 died and for ethical reasons, the 4<sup>th</sup> animal was euthanased and no second treatment was performed.

Under these conditions, the dose of 400 mg/kg/day (x2) was retained as the maximum dose to be tested in the comet assay. Two inferior doses were also tested, *i.e.* 200 and 100 mg/kg/day (x2).

TABLE 1

**in vivo COMET ASSAY IN ISOLATED RAT DUODENUM CELLS  
TOXICITY ASSAY**

<b>SPONSOR:</b>	<b>RHODIA</b>	Species: RAT
<b>TEST ITEM:</b>	<b>CATECHOL</b>	Strain: OFA SPRAGUE DAWLEY
<b>VEHICLE:</b>	Distilled water	Sex: male
<b>DOSING VOLUME:</b>	10 mL/kg	Administration route: oral
<b>ORGAN:</b>	<b>STOMACH</b>	Number of groups: 3
	<b>DUODENUM</b>	Number of animals: 4

**PRELIMINARY ASSAY**

**Dates of treatments**

1<sup>st</sup> treatment: 29/05/07  
 2<sup>nd</sup> treatment: 30/05/07  
 Observation dates: 29/05/07 to 31/05/07

DOSES in mg/kg/day (x2)	DOSING VOLUME	NUMBER OF ANIMALS	% MORTALITY 24 HOURS AFTER FIRST TREATMENT	% MORTALITY 24 HOURS AFTER SECOND TREATMENT
800*	10 mL/kg	4	100	-
400**		4	0	0

\*: 4 animals presented clonic convulsions after the 1<sup>st</sup> treatment. Animals were euthanasied after 30 min.

\*\*: Neither mortality nor strong clinical signs were noted

**CONFIRMATORY ASSAY**

**Dates of treatments**

1<sup>st</sup> treatment: 19/06/07  
 2<sup>nd</sup> treatment: 20/06/07  
 Observation dates: 19/06/07 to 21/06/07

DOSES in mg/kg/day (x2)	DOSING VOLUME	NUMBER OF ANIMALS	% MORTALITY 24 HOURS AFTER FIRST TREATMENT	% MORTALITY 24 HOURS AFTER SECOND TREATMENT
500*	10 mL/kg	4	75	-

\*: 3 animals with strong clonic convulsions and 3 dead after 25 min after the 1<sup>st</sup> treatment  
 4<sup>th</sup> animal euthanasied

#### 4. IN VIVO COMET ASSAY

At least 5 male rats per dose were treated orally twice with 400, 200 and 100 mg/kg/day (x2) **CATECHOL** for the *in vivo* comet assay on stomach and duodenum. The 2 highest doses of 400 and 200 mg/kg/day (x2), giving acceptable cell viability using the Trypan blue vital dye exclusion technique, *i.e.* >70%, were analysed first (See Table 5 and 9, Appendix 1). At sponsor's request, the 3<sup>rd</sup> dose of 100 mg/kg/day (x2), also presenting a cell viability above 70%, was analyzed and the results presented in the Final report.

The test results are summarized in Tables 2 and 3 and in Figures 1 and 2. The tables of data of individual values for nuclei's OTM are presented in Appendix No. 7 for stomach and in Appendix No. 10 for duodenum. The individual results are summarized in Appendix No. 1 (Tables 5 to 8) for stomach cells and appendix No. 2 (Tables 9 to 12) for duodenum cells. The individual representation of distributions is presented in Appendix No. 3 for stomach and No. 5 for duodenum.

The Tables of data of individual values of OTM, Tail Length and % DNA in Tail are presented in Appendices 7, 8 and 9 for the stomach and 10, 11 and 12 for the duodenum.

The historical data for negative control and positive control were constituted with an assay after two treatments followed by one sampling time, 3 to 6 hours after the last treatment.

Significant increases in the mean OTM median values were noted in the groups treated with MNNG and dimethylhydrazine, demonstrating the sensitivity of the animal strain used to specific clastogenic agents on stomach and duodenum. Thus, the validity criteria for the test were fulfilled and the test was valid.

The weight homogeneity of the animals used in this test after random-distribution was verified by comparing the weight mean of the treatment groups with that of the control group (Student t-test) (Table 4). There was no statistically significant difference between the weights of animals treated with the test item and those of control rats.

The results of the cellular viability determination upon the Trypan blue exclusion method are presented in Tables 5 and 9. The calculated relative viabilities for stomach and duodenum cells were superior to 70 %. However, it is to be noted that very strong clonic convulsions were observed 5 minutes after oral administration of **Catéchol** at the dose of 400 mg/kg/day (x2), leading to one death between 30 minutes and 2 hours after the 1<sup>st</sup> treatment. Furthermore, the 4 animals were trembling after the 2<sup>nd</sup> treatment at 400 mg/kg/day. The animals treated with the two inferior doses of 200 and 100 mg/kg/day elicited no clinical signs.

Furthermore, the observation of slides during image analysis of stomach and duodenum cells, showed a very low cell density at the two highest doses analysed of 400 and 200 mg/kg/day (x2). This low cell density indicates the presence of cell lysis that could not be identified with the Trypan blue vital dye exclusion technique nor with the measurement of ghost cells.

#### GENOTOXICITY IN RAT STOMACH CELLS

No statistically significant increase in the OTM medians was observed in rat stomach cells treated with the three doses of **Catéchol**, *i.e.* 400 – 200 and 100 mg/kg/day (x2). Indeed, the values of median OTM for 600 cells were of 0.81 – 0.35 and 1.13 at 400 – 200 and 100 mg/kg/day (x2), respectively, vs. 2.26 in the negative control group (Tables 2 and 6). The OTM medians at the three tested doses were under the value of OTM median for the control group.

The F test (F of Snedecor) showed a statistically significant difference between group OTM variance ( $p < 0.0001$ ). Due to this non-homogeneity of variance between OTM groups, statistical analysis was performed using non-parametric tests.

The non-parametric statistical assessment allowed to display a significant dose-response relationship (Kruskal-Wallis,  $p < 0.0001$ ).

The pair wise analysis using Mann-Whitney showed statistically significant decreases in the median OTM of the three tested doses of 400 – 200 and 100 mg/kg/day (x2), vs. the negative control (Mann-Whitney,  $p < 0.0001$ ). Nevertheless, this decrease had no meaning in terms of genotoxicity.

Regarding the percentages of ghost cells, no increase compared to the negative control was observed (Table 8).

Under these conditions, **Catéchol** was not considered as a DNA strand breaks and/or alkali-labile sites inducer on stomach cells in the rat.

#### **GENOTOXICITY IN RAT DUODENUM CELLS**

Statistically significant increases in the OTM medians were observed in duodenum cells from rats, treated with the doses of 200 and 100 mg/kg/day (x2) of **Catéchol**. Indeed, the values of median OTM for 600 cells (4 animals tested per group) reached 3.38 and 4.64 at the two doses of 200 and 100 mg/kg/day (x2), respectively, vs. 1.48 in the negative control group (Tables 3 and 10). At these two dose-levels of 200 and 100 mg/kg/day (x2), two animals out of the four treated, presented particularly strong increases in the median OTM, with values reaching 6.07 and 4.21 at the dose of 200 mg/kg/day (x2) and 9.73 and 7.29 at the dose of 100 mg/kg/day (x2) (for 150 cells observed by animal, Table 10).

In return, the dose of 400 mg/kg/day (x2) did not induce a statistically significant increase in the median OTM, with a value of 1.28. This value was under the value of OTM median for the control group.

It is noteworthy that the highest median OTM was observed at the lowest dose tested of 100 mg/kg/day (x2). The decrease in the values of median OTM at the two upper doses of 400 and 200 mg/kg/day (x2), compared to the dose of 100 mg/kg/day (x2), is most probably related to toxicity of the test item **Catéchol**, consistent with the clinical signs described above, *i.e.* strong clonic convulsions were observed 5 minutes after oral administration of **Catéchol** at the dose of 400 mg/kg/day (x2), leading to one death between 30 minutes and 2 hours after the 1<sup>st</sup> treatment and the 4 animals were trembling after the 2<sup>nd</sup> treatment at 400 mg/kg/day. In return, no clinical signs were observed after the treatments at 200 and 100 mg/kg.

Furthermore, the cytotoxicity evaluated with the Trypan blue vital exclusion method and the measurement of the percentage of ghost cells during image analysis, did not permit to evaluate the potential cytotoxicity at the three doses tested (Tables 9 and 12).

The bell-shaped curve effect observed is considered as an indicator of the genotoxic activity of **Catechol**.

*No dose without genotoxic effect could be determined at a concentration lower than 100 mg/kg/day (x2).* Therefore, it would be useful to implement a complementary assay in order to investigate if **Catéchol** induces a genotoxic effect at doses lower than 100 mg/kg/day (x2) and to determine the highest dose under 100 mg/kg/day (x2) without genotoxic activity.

Regarding the statistical assessment, the F test (F of Snedecor) showed a statistically significant difference between group OTM variance ( $p < 0.0001$ ). Due to this non-homogeneity of variance between OTM groups, statistical analysis was performed using non-parametric tests.

The non-parametric statistical assessment allowed to display a significant dose-response relationship (Kruskall-Wallis,  $p < 0.0001$ ). It is noteworthy that this is a reverse dose-effect relationship, *i.e.* there is a decrease in the median OTM when increasing the doses of **Catechol**.

The pair wise analysis using Mann-Whitney showed statistically significant increases in the median OTM of the two tested doses of 200 and 100 mg/kg/day (x2), vs. the negative control. In return, the dose of 400 mg/kg/day (x2) did not induce a statistically significant increase in the median OTM.

Regarding the percentages of ghost cells, no increase compared to the negative control was observed (Table 12).

Under these conditions, **Catechol** was considered as a DNA strand breaks and/or alkali-labile sites inducer on duodenum cells in the rat.

**HYPOTHESIS ON THE GENOTOXICITY OF CATECHOL**

The results obtained in the *in vivo* comet assay on **stomach** in presence of **CATECHOL**, *i.e.*:

- no statistically significant increases in DNA strand breaks at non-lethal dose on rat *stomach* cells after oral administration.
- statistically significant decreases in the median OTM of the three tested doses and displaying a significant reverse dose-response relationship
- absence of signs of cytotoxicity at the three doses tested with the Trypan blue vital exclusion method
- no significant increase in the measurement of the percentage of ghost cells on the slides
- very low cell density observed during image analysis indicating a probable cell lysis due to cytotoxicity and /or highly damaged cells with loss of information

and in **duodenum**, *i.e.* :

- statistically significant increases in DNA strand breaks, with the highest increase of median OTM at the lowest dose tested, decrease in the values of median OTM at the two upper doses and no statistically significant increases at the highest dose tested
- displaying a significant reverse dose-response relationship, decrease in the median OTM when increasing the doses of **Catechol**, *i.e.* a bell-shaped curve response.
- absence of signs of cytotoxicity at the three doses tested with the Trypan blue vital exclusion method
- no significant increase in the measurement of the percentage of ghost cells on the slides
- very low cell density observed during image analysis indicating a probable cell lysis due to cytotoxicity and /or highly damaged cells with loss of information

lead to different hypothesis.

**1/ The test item Catechol seems to induce excessive fragmentation of DNA.** This extreme DNA fragmentation may be caused by:

- DNA strand breaks, single or double DNA strand breaks (SSB or DSB).
- Another possible mechanism could be DNA fragilization through the formation of alkali-labile sites. In such cases, the formation of apurinic or apyrimidic sites by excision of damaged bases by a DNA-glycosylase, may alter and fragilize DNA. The alkali-labile sites are stable up to a pH of 12.5 but are eliminated at a pH of 13, as in the *in vivo* rodent alkaline assay, causing DNA strand breaks (Eastman & Barry, 1992).

The difference of genotoxic activity observable in stomach and in duodenum cells may be related to the fact that the concentration of **Catechol** in contact with the tested organ is higher in the stomach than in the duodenum.

The observation of the slides at the two highest doses tested of 400 and 200 mg/kg/day (x2) during image analysis showed a total absence of ghost cells, as well as a very low cell density, that may be related to the total lysis of the cells after DNA fragmentation. The strong pulverization of DNA hindered correct staining of the DNA and thus observation and scoring of comet cells. The limit of detection has been trespassed. Furthermore, the lowest dose tested of 100 mg/kg/day (x2), inducing a genotoxic activity in the comet assay, presented a normal cell density on the slides during image analysis.

The absence of signs of cytotoxicity at the three doses tested using techniques such as Trypan blue vital exclusion method and the measurement of the percentage of ghost cells on the slides may be due to the fact that some ghost cells are not visible on the slides. Indeed, as stated by Burlinson (2007), for certain chemicals, the enhanced DNA migration is not observed in the *in vivo* rodent alkaline comet assay, despite the presence of necrosis or apoptosis in the target organs. In that case, the cytotoxicity is directly exerted by **Catechol**.

**2/ The test item Catechol is most probably an oxidizing agent, producing free radicals damaging DNA.**

In order to show that reactive oxygen species may be involved in the genotoxic activity of **Catechol**, an *in vivo* rodent alkaline (pH>13) comet assay adding a specific endonuclease enzyme, e.g. formamidopyrimidine-DNA glycosylase (Fpg), could be performed at *lower doses* than the ones tested in the current study.

The Fpg enzyme presents a DNA glycosylase activity, associated with an AP lyase activity leading to the formation of AP sites in DNA followed by the formation of single strand DNA breaks. In a normal cell, DNA repair is achieved by the action of other enzymes (DNA polymerase and DNA ligase). Under the conditions of the Comet assay, these enzymes are present until the sacrifice of animals but are absent during the Unwinding, Electrophoresis and staining steps of the Comet Assay. The adjunction of Fpg during the Comet assay allows to increase the number of breaks in DNA induced through an oxidizing mechanism and leads to an increase in comet response in case of DNA oxidative damage induced by **Catechol**.

The expected results after treatment with **Catechol** and addition of Fpg, would be an increase in median OTM values, compared to the OTM values of cells exposed to **Catechol** alone, without addition of Fpg enzyme.

Nevertheless, performing this new comet assay will not modify the results and conclusions of the current study.

The decrease in the median OTM in stomach and duodenum cells when increasing the doses of **Catechol** and the reverse dose-response relationship indicate the possible existence of a bell-shape curved. As described by Burlinson et Al (2007), in some cases it is also possible to detect a decrease in DNA migration, as observed with **Catechol** in stomach and duodenum cells, due to:

- the loss of heavily damaged or dying cells during sample processing or electrophoresis, and /or secondary toxicity induced by **Catechol**.
- The downturn phenomenon in the dose-response curve may also be attributed to an altered bioavailability at higher dose levels.

Due to the bell-shape curve effect of the genotoxic activity of **Catechol**, it is not excluded that **Catechol** may display genotoxic activity both in stomach and duodenum cells at dose-levels lower than 100 mg/kg/day (x2).

**TABLE 2**  
**in vivo COMET ASSAY IN ISOLATED RAT STOMACH CELLS**  
**RECAPITULATIVE TABLE**

<b>SPONSOR:</b>	<b>RHODIA</b>	<b>Species:</b> RAT
<b>TEST ITEM:</b>	<b>Catéchol</b>	<b>Strain:</b> OFA SPRAGUE DAWLEY
<b>VEHICLE:</b>	<b>Distilled water</b>	<b>Sex:</b> male
<b>DOSING VOLUME:</b>	<b>10 mL/kg</b>	<b>Administration route:</b> oral
		<b>Number of groups:</b> 3
		<b>Number of animals:</b> 4

**ORGAN: STOMACH**

1<sup>st</sup> treatment: 25/09/2007

2<sup>nd</sup> treatment\*: 26/09/2007

\* the positive control was treated once at that date

in vivo COMET ASSAY IN ISOLATED RAT STOMACH CELLS							
GROUPS	COMPOUND	DOSES in mg/kg/day (x2)	OTM Median for 600 cells <sup>(1)</sup>	F of Snedecor (homogeneity of variances)	NON PARAMETRIC statistical evaluation		Relative ratio of ghost cells <sup>(4)</sup>
					p kruskal- wallis <sup>(2)</sup>	p Mann- whitney <sup>(3)</sup>	
Solvent control	Distilled water	0	2.26	p<0.0001	p<0.0001	-	-
TREATED	Catéchol	400	0.81			p<0.0001	0.54
		200	0.35			p<0.0001	0.59
		100	1.13			p<0.0001	0.96
Positive control	MNNG	20 mg/kg/day (x1)	5.37	-	-	p<0.0001	0.95

1: For 450 cells in positive control

2: Total group without positive control

3: OTM values obtained in treated group compared to OTM values obtained in solvent control group

4: Corresponds to the percentage of ghost cells per treated group /percentage of ghost cell in negative control group.

**TABLE 3**  
**in vivo COMET ASSAY IN ISOLATED RAT DUODENUM CELLS**  
**RECAPITULATIVE TABLE**

SPONSOR:	RHODIA	Species: RAT
TEST ITEM:	CATECHOL	Strain: OFA SPRAGUE DAWLEY
VEHICLE:	Distilled water	Sex: male
DOSING VOLUME:	10 mL/kg	Administration route: oral
		Number of groups: 3
		Number of animals: 4

**ORGAN: DUODENUM**

1<sup>st</sup> treatment: 25/09/2007

2<sup>nd</sup> treatment\*: 26/09/2007

\* the positive control was treated once at that date

in vivo COMET ASSAY IN ISOLATED RAT DUODENUM CELLS							
GROUPS	COMPOUND	DOSES in mg/kg/day (x2)	OTM Median for 600 cells <sup>(1)</sup>	F of Snedecor (homogeneity of variances)	NON PARAMETRIC statistical evaluation		Relative ratio of ghost cells <sup>(4)</sup>
					p kruskal- wallis <sup>(2)</sup>	p Mann- whitney <sup>(3)</sup>	
Solvent control	Distilled water	0	1.48	p<0.0001	p<0.0001	-	-
TREATED	Catéchol	400	1.28			N.S.	0.79
		200	3.38			p<0.0001	0.94
		100	4.64			p<0.0001	1.10
Positive control	Dimethylhydrazine	20 mg/kg/day (x1)	8.94	-	-	p<0.0001	0.87

1: For 450 cells in positive control

2: Total group without positive control

3: OTM values obtained in treated group compared to OTM values obtained in solvent control group

4: Corresponds to the percentage of ghost cells per treated group /percentage of ghost cell in negative control group

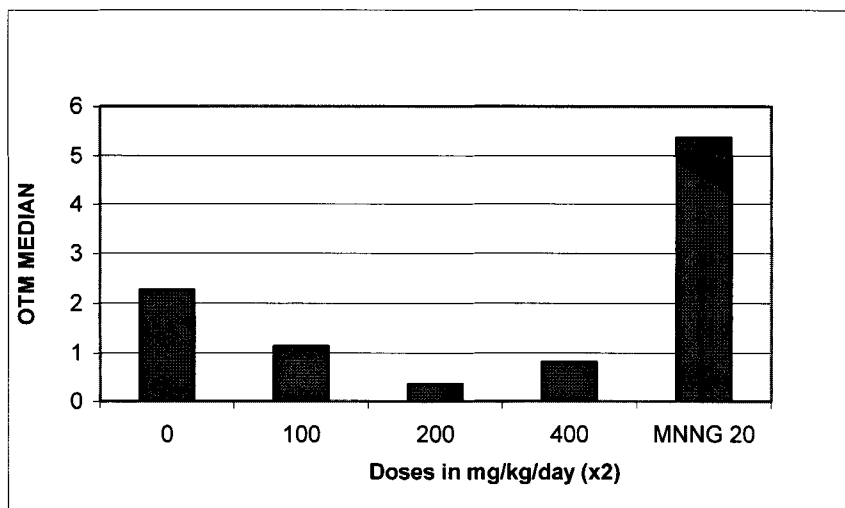
**FIGURE 1**  
**in vivo COMET ASSAY IN ISOLATED RAT STOMACH CELLS**

**OTM MEDIAN per group**

<b>SPONSOR:</b>	<b>RHODIA</b>	Species: RAT
<b>TEST ITEM:</b>	<b>Catéchol</b>	Strain: OFA SPRAGUE DAWLEY
<b>VEHICLE:</b>	<b>Distilled water</b>	Sex: male
<b>DOSING VOLUME:</b>	<b>10 mL/kg</b>	Administration route: oral
		Number of groups: 3
		Number of animals: 4

**ORGAN: STOMACH**

1<sup>st</sup> treatment: 25/09/2007  
2<sup>nd</sup> treatment\*: 26/09/2007  
\* the positive control was treated once at that date



**Conclusion:**

A statistically significant linear trend in nuclear fragmentation, excluding positive control was revealed by the Kruskal-Wallis test. The analysis showed a statistically significant dose-related decrease in the median OTM at the three tested doses of 400 – 200 and 100 mg/kg/day (x2). The trend had hence no meaning in terms of genotoxicity.

**FIGURE 2**  
**in vivo COMET ASSAY IN ISOLATED RAT DUODENUM CELLS**

**OTM MEDIAN per group**

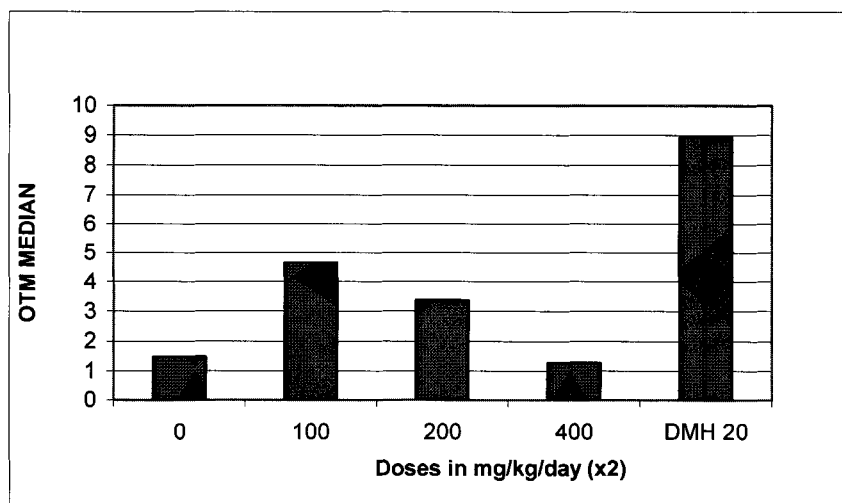
<b>SPONSOR:</b>	<b>RHODIA</b>	Species: RAT
<b>TEST ITEM:</b>	<b>CATECHOL</b>	Strain: OFA SPRAGUE DAWLEY
<b>VEHICLE:</b>	Distilled water	Sex: male
<b>DOSING VOLUME:</b>	10 mL/kg	Administration route: oral
		Number of groups: 3
		Number of animals: 4

**ORGAN: DUODENUM**

1<sup>st</sup> treatment: 25/09/2007

2<sup>nd</sup> treatment\*: 26/09/2007

\* the positive control was treated once at that date



**Conclusion:**

A statistically significant linear trend in nuclear fragmentation, excluding positive control was revealed by the Kruskal-Wallis test.

**D. CONCLUSION**

The test item CATECHOL (batch FPC0619301) provided by RHODIA was investigated by the means of the *in vivo* comet assay on stomach and duodenum, under alkaline conditions (SCGE) in the male OFA Sprague Dawley rats treated orally twice with 400, 200 and 100 mg/kg/day, with one sampling time 3 to 6 hours after the last treatment. Following the results of the toxicity assay, the maximum tolerated dose (MTD) determined was of 400 mg/kg/day. This dose was retained as the maximum dose to be tested, as well as two lower doses corresponding to MTD/2 and MTD/4. These two doses were not toxic, indeed, no clinical signs were observed.

Under these experimental conditions, CATECHOL induced no statistically significant increases in DNA strand breaks at non-lethal dose on rat *stomach* cells after oral administration. CATECHOL is hence devoid of genotoxic activity on the *stomach*.

In return, CATECHOL induced statistically significant increases in DNA strand breaks at non-lethal doses on rat *duodenum* cells after oral administration, with the highest increase of median OTM at the lowest dose tested of 100 mg/kg/day (x2). Furthermore, the very low cell density observed at the two highest doses tested during image analysis, indicates a probable cell lysis due to cytotoxicity and /or highly damaged cells with loss of information. Regarding the criteria described in paragraph 9, a test item is found to demonstrate genotoxic properties against the target organ if it results in a statistically significant increase in the OTM median compared with the negative control group and if the genotoxicity detected shows a dose-effect relationship. In fact the results showed a statistically significant increase in the median OTM, but with an inverse dose-effect relation, with a bell-shaped curve response. The test item Catechol was thus considered as genotoxic on rat duodenum cells.

It would be useful to implement a complementary assay under the same experimental conditions on duodenum cells only, but using doses lower than 100 mg/kg/day (x2), in order to determine if there is a high dose without genotoxic effect under the dose level of 100 mg/kg/day (x2). Under these conditions, CATECHOL was considered as a DNA strand breaks and/or alkali-labile sites inducer on *duodenum* cells.

A satisfactory agreement was observed between the actual and nominal concentrations of CATECHOL in treatment solutions used in the *in vivo* comet assay performed on stomach and duodenum. Indeed, the deviations from nominal concentrations were within an acceptable range of  $\pm 10\%$ .

## **E. REFERENCES**

**Ashby J.**, Tinwell H., Lefevre P.A., Browne M.A.

The single cell gel electrophoresis assay for induced DNA damage (comet assay): measurement of tail length and moment

Mutagenesis 10 (1995) 85-90.

**Bauer E.**, Recknagel R.D., Fiedler U., Wollweber L., Bock C., Greulich K.O.

The distribution of the tail moment in single cell gel electrophoresis (comet assay) obeys a chi-square ( $\chi^2$ ) not a gaussian distribution

Mutat. Res. 398 (1998) 101-110.

**Brault D.**, Renault D, Tombolan F, Thybaud V. Kinetics of induction of DNA damage and lacZ gene mutations in stomach mucosa of mice treated with beta-propiolactone and N-methyl-N'-nitro-N-nitrosoguanidine, using single-cell gel electrophoresis and Mutamouse models.

Environ Mol Mutagen. 1999;34(2-3):182-9.

**Burlinson B.** An in vivo unscheduled DNA synthesis (UDS) assay in the rat gastric mucosa: preliminary development.

Carcinogenesis. 1989 Aug;10(8):1425-8.

**Burlinson B.**, Tice RR, Speit G, Agurell E. et al.

Fourth International Workgroup on Genotoxicity testing: results of the *in vivo* comet assay workgroup.

Mutat Res 627 (2007) 31-5

**Eastman A.**, Barry MA.

The origins of DNA breaks: a consequence of DNA damage, DNA repair, or apoptosis?

Cancer Invest. 1992; 10(3): 229-40.

**Evans GS**, Flint N, Somers AS, Eyden B, Potten CS. The development of a method for the preparation of rat intestinal epithelial cell primary cultures.

J Cell Sci. 1992 Jan;101 ( Pt 1):219-31.

**Fielder R.J.**, Allen J.A., Boobis A.R., Botham P.A., Doe J., Esdaile D.J., Gathehouse D.G., Hosdon-Walker G., MORTON D.B., Kirkland D.J. and Richold M.

Dose setting in vivo mutagenicity assays

Mutagenesis, 7 (1992), 313- 319.

**Fairbairn D.W.**, Olive P.L., O'Neill K.L.

The comet assay: a comprehensive review

Mutat. Res. 339 (1995) 37-59.

**Hartmann A.**, Schumacher M, Plappert-Helbig U, Lowe P, Suter W, Mueller L. Use of the alkaline in vivo Comet assay for mechanistic genotoxicity investigations.

Mutagenesis. 2004 Jan;19(1):51-9.

**Hellman B.**, Vaghef H., Boström B.

The concepts of tail moment and tail inertia in the single cell gel electrophoresis assay

Mutat. Res. 336 (1995) 123-131.

**McKelvey-Martin V.J.**, Green M.H.L., Schmezer P., Pool-Zobel B.L., De Méo M.P., Collins A.

The single cell gel electrophoresis assay (comet assay): a European review

Mutat. Res. 288 (1993) 47-63.

**Olive P.L.**, Banath J.P., Durand R.E.

Heterogeneity in radiation-induced DNA damage and repair in tumor and normal cells measured using the "comet" assay

Radiat. Res. 122 (1990) 86-94.

**Ostling O.**, Johanson K. J.

Microelectrophoretic study of radiation-induced DNA damages in individual mammalian cells

Biochem. Biophys. Res. Commun. 123 (1984) 291-298.

**Rojas E.**, Lopez M.C., Valverde M.

Single cell gel electrophoresis assay: methodology and applications  
J. Chromatogr. 722 (1999) 225-254.

**Singh N.P.**, McCoy M.T., Tice R.R., Schneider E.L

A simple technique for quantification of low levels of DNA damage in individual cells  
Exp. Cell Res. 175 (1988) 184-191.

**Tice R.R.**, Strauss G.H.

The single cell gel electrophoresis/comet assay: a potential tool for detecting radiation-induced DNA damage in humans  
Stem Cells 13 (1995) 207-214.

**Tice R.R.**, Agurell E., Anderson D., Burlinson B., Hartmann A., Kobayashi H., Miyamae Y., Rojas E., Ryu J.C., Sasaki Y.F.

Single cell gel/comet assay: guidelines for *In vivo* and *in vivo* genetic toxicology testing, Environ. Mol. Mutagen. 35 (2000) 206-221.

**Woods J.A.**, O'Leary K.A., McCarthy R.P., O'Brien N.M.

Preservation of comet assay slides: comparison with fresh slides  
Mutat. Res. 429 (1999) 181-187.

**Appendix No. 1: Individual results for the stomach**

TABLE 4

## in vivo COMET ASSAY IN ISOLATED RAT STOMACH and DUODENUM CELLS

## ANIMAL WEIGHT

SPONSOR: RHODIA  
 TEST ITEM: CATECHOL  
 VEHICLE: Distilled water  
 DOSING: 10 mL/kg  
 VOLUME:

Species: RAT  
 Strain: OFA SPRAGUE DAWLEY  
 Sex: male  
 Administration route: oral  
 Number of groups: 3  
 Number of animals: 4

ORGAN: STOMACH  
 DUODENUM

1<sup>st</sup> treatment: 25/09/2007  
 2<sup>nd</sup> treatment\*: 26/09/2007

Negative control group		TREATED GROUPS						Stomach Positive control group		Duodenum Positive control group	
Distilled water		DOSES in mg/kg/day (x2)						MNNG		Dimethylhydrazine	
0		400		200		100		20 mg/kg/day (x1)		20 mg/kg/day (x1)	
Animal number	Weight (g)	Animal number	Weight (g)	Animal number	Weight (g)	Animal number	Weight (g)	Animal number	Weight (g)	Animal number	Weight (g)
6511	185	6516	173	6521	160	6526	176	6531	163	6535	177
6512	188	6517	178	6522	180	6527	160	6532	177	6536	168
6513	167	6518	157	6523	178	6528	169	6533	172	6537	167
6514	185	6519	186	6524	185	6529	179	6534	182	6538	192
6515	180	6520	178	6525	161	6530	156	-	-	-	-

\*: The positive control was treated once at that date

Mean	181		174.4		172.8		168.0		173.5		176
Sd	8.34		10.78		11.52		9.92		8.10		11.58
t			0.97		1.15		1.77		1.20		0.66
p			N.S		N.S		N.S		N.S		N.S

TABLE 5

## in vivo COMET ASSAY IN ISOLATED RAT STOMACH CELLS

## DETERMINATION OF THE VIABILITY OF THE ISOLATED RAT STOMACH CELLS

**SPONSOR:** RHODIA Species: RAT  
**TEST ITEM:** Catéchol Strain: OFA SPRAGUE DAWLEY  
**VEHICLE:** Distilled water Sex: male  
**DOSING VOLUME:** 10 mL/kg Administration route: oral  
 Number of groups: 3  
 Number of animals: 4

**ORGAN:** STOMACH

1st treatment: 25/09/2007

2nd treatment\*: 26/09/2007

\*: The positive control was treated once at that date.

Solvent control	COMPOUND	DOSES in mg/kg/day (x2)	Animal number	Percentage of viability (%)	Relative viability compared to solvent control (%)
Solvent control	Distilled water	0	6511	100.0	-
			6512	100.0	
			6513	(a)	
			6514	100.0	
			6515	100.0	
TREATED	Catéchol	400	6516	(a)	(a)
			6517	100.0	100.0
			6518	100.0	100.0
			6519	94.4	94.4
			6520	100.0	100.0
		200	6521	100.0	100.0
			6522	98.3	98.3
			6523	(a)	(a)
			6524	97.5	97.5
			6525	100.0	100.0
		100	6526	98.0	98.0
			6527	94.7	94.7
			6528	(a)	(a)
			6529	100.0	100.0
			6530	100.0	100.0
Positive control	MNNG	20 mg/kg/day (x1)	6531	100.0	100.0
			6532	100.0	100.0
			6533	(a)	(a)
			6534	93.9	93.9

(a): Animal not used for the genotoxicity assay

TABLE 6

**in vivo COMET ASSAY IN ISOLATED RAT STOMACH CELLS**  
**OLIVE TAIL MOMENT MEDIANS PER ANIMAL AND PER GROUP**

**SPONSOR:** RHODIA  
**TEST ITEM:** Catéchol  
**VEHICLE:** Distilled water  
**DOSING VOLUME:** 10 mL/kg

Species: RAT  
 Strain: OFA SPRAGUE DAWLEY  
 Sex: male  
 Administration route: oral  
 Number of groups: 3  
 Number of animals: 4

**ORGAN:** STOMACH

1st treatment: 25/09/2007  
 2nd treatment\*: 26/09/2007  
 \*. The positive control was treated once at that date

GROUPS	COMPOUND	DOSES in mg/kg/day (x2)	Animal 1	Animal 2	Animal 3	Animal 4	Total group (4 animals)
			Median for 150 cells	Median for 150 cells	Median for 150 cells	Median for 150 cells	Median for 600 cells*
Solvent control	Distilled water	0	1.74	1.14	8.86	2.53	2.26
TREATED	Catéchol	400	5.45	0.45	2.51	0.13	0.81
		200	0.21	0.18	0.80	0.60	0.35
		100	0.96	1.49	1.02	1.26	1.13
Positive control	MNNG	20 mg/kg/day (x1)	24.89	9.28	1.08	-	5.37

\*: Median for 450 cells in positive control

**TABLE 7**  
**in vivo COMET ASSAY IN ISOLATED RAT STOMACH CELLS**  
**OLIVE TAIL MOMENT MEDIAN PER SLIDE, PER ANIMAL AND PER GROUP**

SPONSOR:  
 TEST ITEM:  
 VEHICLE:  
 DOSING VOLUME

RHODIA  
 Catéchol  
 Distilled water  
 10 mL/kg

Species: RAT  
 Strain: OFA SPRAGUE DAWLEY  
 Sex: male  
 Administration route: oral  
 Number of groups: 3  
 Number of animals: 4  
 1<sup>st</sup> treatment: 25/09/2007  
 2<sup>nd</sup> treatment\*: 26/09/2007

ORGAN: STOMACH

\*: The positive control was treated once at that date.

GROUPS	COMPOUND	DOSES in mg/kg/day (x2)	Animal number	Slide number BC-07-	Number of analysed cells /slide	Number of analysed cells /animal	Olive Tail Moment		
							per slide	per animal	per GROUP
							Median (/50 cells)	Median (/150 cells)	Median (/600 cells)
Solvent control	Distilled water	0	6512	213 A	50	150	1.74	1.74	2.26
				213 B	50		0.78		
				213 C	50		3.00		
			6514	214 A	50	150	1.96	1.14	
				214 B	50		0.83		
				214 C	50		0.74		
			6511	215 A	50	150	11.60	8.86	
				215 B	50		15.07		
				215 C	50		2.64		
			6515	216 A	50	150	2.97	2.53	
				216 B	50		1.21		
				216 C	50		3.84		
TREATED	Catéchol	400	6518	220 A	50	150	5.99	5.45	0.81
				220 B	50		6.29		
				220 C	50		4.70		
			6517	221 A	50	150	0.36	0.45	
				221 B	50		0.90		
				221 C	50		0.40		
			6520	222 A	50	150	4.67	2.51	
				222 B	50		3.02		
				222 C	50		1.31		
			6519	223 A	50	150	0.08	0.13	
				223 B	50		0.16		
				223 C	50		0.14		
		200	6524	224 A	50	150	0.20	0.21	0.35
				224 B	50		0.18		
				224 C	50		0.30		
			6521	225 A	50	150	0.10	0.18	
				225 B	50		0.18		
				225 C	50		0.47		
			6522	226 A	50	150	1.52	0.80	
				226 B	50		1.10		
				226 C	50		0.60		
			6525	227 A	50	150	0.65	0.60	
				227 B	50		0.41		
				227 C	50		1.06		
		100	6527	228 A	50	150	0.86	0.96	1.13
				228 B	50		1.20		
				228 C	50		0.93		
			6529	229 A	50	150	0.76	1.49	
				229 B	50		2.41		
				229 C	50		1.53		
			6526	230 A	50	150	1.76	1.02	
				230 B	50		0.56		
				230 C	50		1.61		
			6530	231 A	50	150	1.18	1.26	
				231 B	50		0.75		
				231 C	50		1.76		
Positive control	MNNG	20 mg/kg/day (x1)	6534	217 A	50	150	24.73	24.89	5.37
				217 B	50		24.89		
				217 C	50		24.77		
			6532	218 A	50	150	5.09	9.28	
				218 B	50		6.65		
				218 C	50		16.05		
			6531	219 A	50	150	1.27	1.08	
				219 B	50		1.22		
				219 C	50		0.98		

**TABLE 8**  
**in vivo COMET ASSAY IN ISOLATED RAT STOMACH CELLS**  
**PERCENTAGE OF GHOST CELLS PER ANIMAL AND PER GROUP**

SPONSOR:  
 TEST ITEM:  
 VEHICLE  
 DOSING VOLUME:

RHODIA  
 Catéchol  
 Distilled water  
 10 mL/kg

Species: RAT  
 Strain: OFA SPRAGUE DAWLEY  
 Sex: male  
 Administration route: oral  
 Number of groups: 3  
 Number of animals: 4  
 1<sup>st</sup> treatment: 25/09/2007  
 2<sup>nd</sup> treatment\*: 26/09/2007

ORGAN: STOMACH

\*. The positive control was treated once at that date

GROUPS	COMPOUND	DOSES in mg/kg/day (x2)	Animal number	Slide number BC-07-	Number of ghost cells per slide	Percentage of ghost cells per			Relative ratio of ghost cells <sup>(2)</sup>			
						per slide	per animal	per GROUP <sup>(1)</sup>				
Solvent control	Distilled water	0	6512	213 A	17	25.4	22.41	24.18	-			
				213 B	7	12.3						
				213 C	21	29.6						
			6514	214 A	20	28.6	23.54					
				214 B	17	25.4						
				214 C	10	16.7						
			6511	215 A	21	29.6	28.22					
				215 B	19	27.5						
				215 C	19	27.5						
			6515	216 A	12	19.4	22.57					
				216 B	18	26.5						
				216 C	14	21.9						
TREATED	Catéchol	400	6518	220 A	6	10.7	13.74	13.15	0.54			
				220 B	9	15.3						
				220 C	9	15.3						
			6517	221 A	3	5.7	10.07					
				221 B	7	12.3						
				221 C	7	12.3						
			6520	222 A	12	19.4	17.06					
				222 B	11	18.0						
				222 C	8	13.8						
			6519	223 A	7	12.3	11.72					
				223 B	5	9.1						
				223 C	8	13.8						
			200	6524	224 A	5	9.1			9.40	14.30	0.59
					224 B	9	15.3					
					224 C	2	3.8					
				6521	225 A	8	13.8			16.60		
					225 B	12	19.4					
					225 C	10	16.7					
		6522		226 A	8	13.8	15.57					
				226 B	13	20.6						
				226 C	7	12.3						
		6525	227 A	7	12.3	15.63						
			227 B	12	19.4							
			227 C	9	15.3							
		100	6527	228 A	13	20.6	22.75	23.15	0.96			
				228 B	11	18.0						
				228 C	21	29.6						
			6529	229 A	27	35.1	28.97					
				229 B	18	26.5						
				229 C	17	25.4						
			6526	230 A	16	24.2	20.51					
				230 B	13	20.6						
				230 C	10	16.7						
			6530	231 A	8	13.8	20.37					
				231 B	15	23.1						
				231 C	16	24.2						
Postitive control	MNNG		20 mg/kg/day (x1)	6534	217 A	12	19.4			25.34	22.92	0.95
					217 B	24	32.4					
					217 C	16	24.2					
				6532	218 A	16	24.2			21.62		
					218 B	9	15.3					
					218 C	17	25.4					
		6531		219 A	16	24.2	21.78					
				219 B	15	23.1						
				219 C	11	18.0						

1: Percentage for 600 cells for solvent control and treated groups, for 450 cells for positive control group

2: Corresponds to the percentage of ghost cells per treated group /percentage of ghost cell in negative control group.

## Appendix No. 2: Individual results for the duodenum

TABLE 9

## in vivo COMET ASSAY IN ISOLATED RAT DUODENUM CELLS

## DETERMINATION OF THE VIABILITY OF THE ISOLATED RAT DUODENUM CELLS

**SPONSOR:** RHODIA Species: RAT  
**TEST ITEM:** CATECHOL Strain: OFA SPRAGUE DAWLEY  
**VEHICLE:** Distilled water Sex: male  
**DOSING VOLUME:** 10 mL/kg Administration route: oral  
 Number of groups: 3  
 Number of animals: 4

**ORGAN:** DUODENUM

1st treatment: 25/09/2007

2nd treatment\*: 26/09/2007

\*: The positive control was treated once at that date.

Solvent control	COMPOUND	DOSES in mg/kg/day (x2)	Animal number	Percentage of viability (%)	Relative viability compared to solvent control (%)
Solvent control	Distilled water	0	6511	94.1	-
			6512	94.3	
			6513	(a)	
			6514	90.3	
			6515	91.9	
TREATED	CATECHOL	400	6516	(a)	(a)
			6517	93.4	100.8
			6518	94.1	101.6
			6519	89.4	96.5
			6520	92.5	99.8
		200	6521	91.6	98.9
			6522	89.2	96.3
			6523	(a)	(a)
			6524	91.6	98.9
			6525	89.4	96.5
		100	6526	92.8	100.2
			6527	91.0	98.2
			6528	(a)	(a)
			6529	93.1	100.5
			6530	95.2	102.8
Positive control	Dimethylhydrazine	20 mg/kg/day (x1)	6535	88.4	95.4
			6536	(a)	(a)
			6537	92.8	100.1
			6538	91.4	98.7

(a): Animal not used for the genotoxicity assay

TABLE 10

**in vivo COMET ASSAY IN ISOLATED RAT DUODENUM CELLS**  
**OLIVE TAIL MOMENT MEDIANS PER ANIMAL AND PER GROUP**

<b>SPONSOR:</b>	<b>RHODIA</b>	Species: RAT
<b>TEST ITEM:</b>	<b>CATECHOL</b>	Strain: OFA SPRAGUE DAWLEY
<b>VEHICLE:</b>	Distilled water	Sex: male
<b>DOSING VOLUME:</b>	10 mL/kg	Administration route: oral
		Number of groups: 3
		Number of animals: 4

**ORGAN: DUODENUM**

1st treatment: 25/09/2007

2nd treatment\*: 26/09/2007

\*: The positive control was treated once at that date

GROUPS	COMPOUND	DOSES in mg/kg/day (x2)	Animal 1	Animal 2	Animal 3	Animal 4	Total group (4 animals)
			Median for 150 cells	Median for 150 cells	Median for 150 cells	Median for 150 cells	Median for 600 cells*
Solvent control	Distilled water	0	1.25	1.58	4.58	0.48	1.48
TREATED	CATECHOL	400	0.90	2.18	0.59	1.60	1.28
		200	1.43	2.23	6.07	4.21	3.38
		100	9.73	7.29	3.12	2.49	4.64
Positive control	Dimethylhydra zine	20 mg/kg/day (x1)	9.37	11.19	7.37	-	8.94

\*: Median for 450 cells in positive control

**TABLE 11**  
**In vivo COMET ASSAY IN ISOLATED RAT DUODENUM CELLS**  
**OLIVE TAIL MOMENT MEDIAN PER SLIDE, PER ANIMAL AND PER GROUP**

SPONSOR:  
 TEST ITEM:  
 VEHICLE:  
 DOSING VOLUME:

RHODIA  
 CATECHOL  
 Distilled water  
 10 mL/kg

Species: RAT  
 Strain: OFA SPRAGUE DAWLEY  
 Sex: male  
 Administration route: oral  
 Number of groups: 3  
 Number of animals: 4  
 1<sup>st</sup> treatment: 25/09/2007  
 2<sup>nd</sup> treatment\*: 26/09/2007

ORGAN: DUODENUM

\*. The positive control was treated once at that date

GROUPS	COMPOUND	DOSES in mg/kg/day (x2)	Animal number	Slide number BC-07-	Number of analysed cells /slide	Number of analysed cells /animal	Olive Tail Moment		
							per slide	per animal	per GROUP
							Median (/50 cells)	Median (/150 cells)	Median (/600 cells)
Solvent control	Distilled water	0	6512	232 A	50	150	1.31	1.25	1.48
				232 B	50		1.11		
				232 C	50		1.77		
			6514	233 A	50	150	0.37	1.58	
				233 B	50		2.94		
				233 C	50		1.80		
			6511	234 A	50	150	12.09	4.58	
				234 B	50		1.56		
				234 C	50		4.70		
			6515	235 A	50	150	0.97	0.48	
				235 B	50		0.20		
				235 C	50		0.98		
TREATED	CATECHOL	400	6518	239 A	50	150	0.91	0.90	1.28
				239 B	50		0.66		
				239 C	50		0.96		
			6517	240 A	50	150	0.87	2.18	
				240 B	50		6.03		
				240 C	50		1.50		
			6520	241 A	50	150	0.20	0.59	
				241 B	50		1.57		
				241 C	50		0.60		
			6519	242 A	50	150	3.89	1.60	
				242 B	50		1.10		
				242 C	50		1.27		
		200	6524	243 A	50	150	4.12	1.43	3.38
				243 B	50		0.79		
				243 C	50		1.76		
			6521	244 A	50	150	3.03	2.23	
				244 B	50		0.83		
				244 C	50		3.14		
			6522	245 A	50	150	11.84	6.07	
				245 B	50		4.22		
				245 C	50		6.65		
			6525	246 A	50	150	5.07	4.21	
				246 B	50		1.61		
				246 C	50		7.01		
		100	6527	247 A	50	150	21.97	9.73	4.64
				247 B	50		7.64		
				247 C	50		5.94		
			6529	248 A	50	150	13.42	7.29	
				248 B	50		5.16		
				248 C	50		6.63		
			6526	249 A	50	150	8.44	3.12	
				249 B	50		3.78		
				249 C	50		1.21		
			6530	250 A	50	150	2.08	2.49	
				250 B	50		1.98		
				250 C	50		3.74		
Positive control	Dimethylhydrazine	20 mg/kg/day (x1)	6535	236 A	50	150	8.89	9.37	8.94
				236 B	50		9.22		
				236 C	50		11.20		
			6537	237 A	50	150	15.18	11.19	
				237 B	50		6.95		
				237 C	50		8.70		
			6538	238 A	50	150	7.32	7.37	
				238 B	50		4.48		
				238 C	50		13.27		

**TABLE 12**  
**in vivo COMET ASSAY IN ISOLATED RAT DUODENUM CELLS**  
**PERCENTAGE OF GHOST CELLS PER ANIMAL AND PER GROUP**

SPONSOR:  
 TEST ITEM:  
 VEHICLE:  
 DOSING VOLUME:

RHODIA  
 CATECHOL  
 Distilled water  
 10 mL/kg

Species: RAT  
 Strain: OFA SPRAGUE DAWLEY  
 Sex: male  
 Administration route: oral  
 Number of groups 3  
 Number of animals 4  
 1<sup>st</sup> treatment: 25/09/2007  
 2<sup>nd</sup> treatment\*: 26/09/2007

ORGAN: DUODENUM

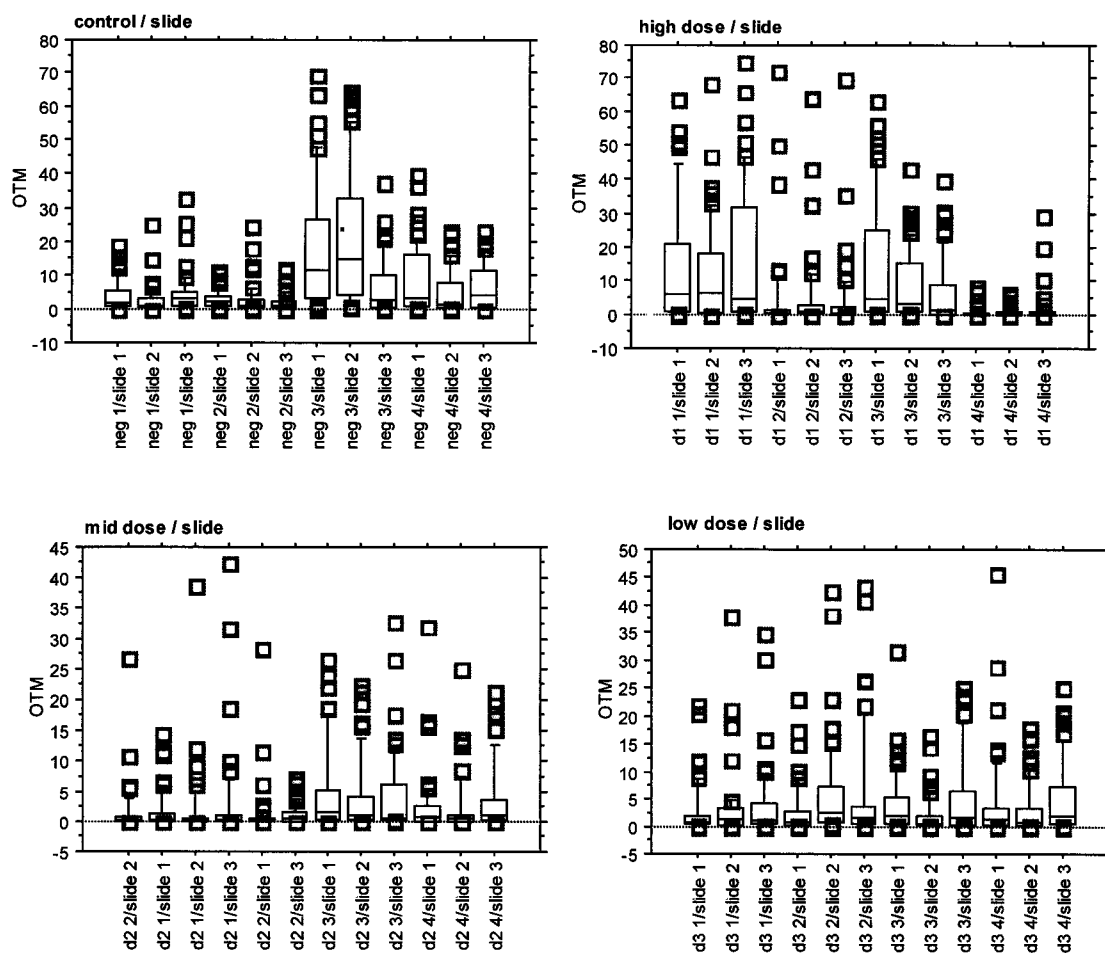
\*: The positive control was treated once at that date

GROUPS	COMPOUND	DOSES in mg/kg/day (x2)	Animal number	Slide number BC-07-	Number of ghost cells per slide	Percentage of ghost cells per			Relative ratio of ghost cells <sup>(2)</sup>
						per slide	per animal	per GROUP <sup>(1)</sup>	
Solvent control	Distilled water	0	6512	232 A	4	7.4	15.39	18.70	-
				232 B	18	26.5			
				232 C	7	12.3			
			6514	233 A	7	12.3	21.97		
				233 B	22	30.6			
				233 C	15	23.1			
			6511	234 A	24	32.4	22.20		
				234 B	7	12.3			
				234 C	14	21.9			
			6515	235 A	9	15.3	15.24		
				235 B	8	13.8			
				235 C	10	16.7			
TREATED	CATECHOL	400	6518	239 A	6	10.7	14.12	14.72	0.79
				239 B	7	12.3			
				239 C	12	19.4			
			6517	240 A	10	16.7	17.56		
				240 B	12	19.4			
				240 C	10	16.7			
			6520	241 A	12	19.4	17.09		
				241 B	10	16.7			
				241 C	9	15.3			
			6519	242 A	4	7.4	10.10		
				242 B	8	13.8			
				242 C	5	9.1			
		200	6524	243 A	13	20.6	16.64	17.64	0.94
				243 B	14	21.9			
				243 C	4	7.4			
			6521	244 A	9	15.3	17.52		
				244 B	13	20.6			
				244 C	10	16.7			
			6522	245 A	12	19.4	17.84		
				245 B	7	12.3			
				245 C	14	21.9			
			6525	246 A	18	26.5	18.58		
				246 B	4	7.4			
				246 C	14	21.9			
		100	6527	247 A	23	31.5	26.81	20.57	1.10
				247 B	21	29.6			
				247 C	12	19.4			
			6529	248 A	11	18.0	28.35		
				248 B	11	18.0			
				248 C	48	49.0			
			6526	249 A	16	24.2	14.45		
				249 B	9	15.3			
				249 C	2	3.8			
			6530	250 A	5	9.1	12.68		
				250 B	7	12.3			
				250 C	10	16.7			
Positive control	Dimethylhydrazine	20 mg/kg/day (x1)	6535	236 A	7	12.3	15.63	16.26	0.87
				236 B	12	19.4			
				236 C	9	15.3			
			6537	237 A	6	10.7	15.58		
				237 B	12	19.4			
				237 C	10	16.7			
			6538	238 A	12	19.4	17.56		
				238 B	10	16.7			
				238 C	10	16.7			

1. Percentage for 600 cells for solvent control and treated groups, for 450 cells for positive control group

2. Corresponds to the percentage of ghost cells per treated group /percentage of ghost cell in negative control group.

## Appendix No. 3: Individual representation of distributions / Stomach



High dose d1 : 400 mg/kg/day (x2)

Mid dose d2 : 200 mg/kg/day (x2)

Low dose d3 : 100 mg/kg/day (x2)

**Appendix No. 4: Non-parametric statistical analysis / Stomach****□ F OF SNEDECOR: HOMOGENEITY BETWEEN GROUP VARIANCES / STOMACH****F test for OTM**

Total group w/o positive control

	Variance Ratio	Num. DDL	Denom DDL	F	p
1, 2	6.094	599	598	6.094	<.0001
1, 3	3.982	599	599	3.982	<.0001
1, neg	1.489	599	599	1.489	<.0001
2, 3	.653	598	599	.653	<.0001
2, neg	.244	598	599	.244	<.0001
3, neg	.374	599	599	.374	<.0001

**Group OTM**

Total group w/o positive control

	Number	Mean	Variance	Std dev	Std Error
1	600	7.095	185.007	13.602	.555
2	599	2.457	30.358	5.510	.225
3	600	3.886	46.460	6.816	.278
neg	600	6.982	124.227	11.146	.455

**□ KRUSKAL-WALLIS / STOMACH**

DDL	3
# Groupes	4
# ex-aequo	1
H	174.038
P value	<.0001
Corrected H for ex-aequo	174.038
Corrected p for ex-aequo	<.0001
450 omitted occurrences	

	Number	Sum of Ranks	Mean of Ranks
1	600	713386.000	1188.977
2	599	551162.000	920.137
3	600	749130.500	1248.551
neg	600	865121.500	1441.869

450 omitted occurrences

□ **MANN-WHITNEY / STOMACH**

• **CONTROL vs. HIGH DOSE**

**Mann-Whitney U for OTM**  
**control vs. high dose**

U	145213.000
U'	214787.000
Z value	-5.795
P value	<.0001
Corrected Z for ex-aequo	-5.795
Corrected p for ex-aequo	<.0001
# ex-aequo	1

1649 omitted occurrences

	Number	Sum of Ranks	Mean of Ranks
1	600	325513.000	542.522
neg	600	395087.000	658.478

1649 omitted occurrences

• **CONTROL vs. MID DOSE**

**Mann-Whitney U for OTM**  
**control vs. mid dose**

U	102553.000
U'	256847.000
Z value	-12.869
P value	<.0001
Corrected Z for ex-aequo	-12.869
Corrected p for ex-aequo	<.0001
# ex-aequo	1

1650 omitted occurrences

	Number	Sum of Ranks	Mean of Ranks
2	599	282253.000	471.207
neg	600	437147.000	728.578

1650 omitted occurrences

- **CONTROL vs. LOW DOSE**

Mann-Whitney U for OTM  
control vs. low dose

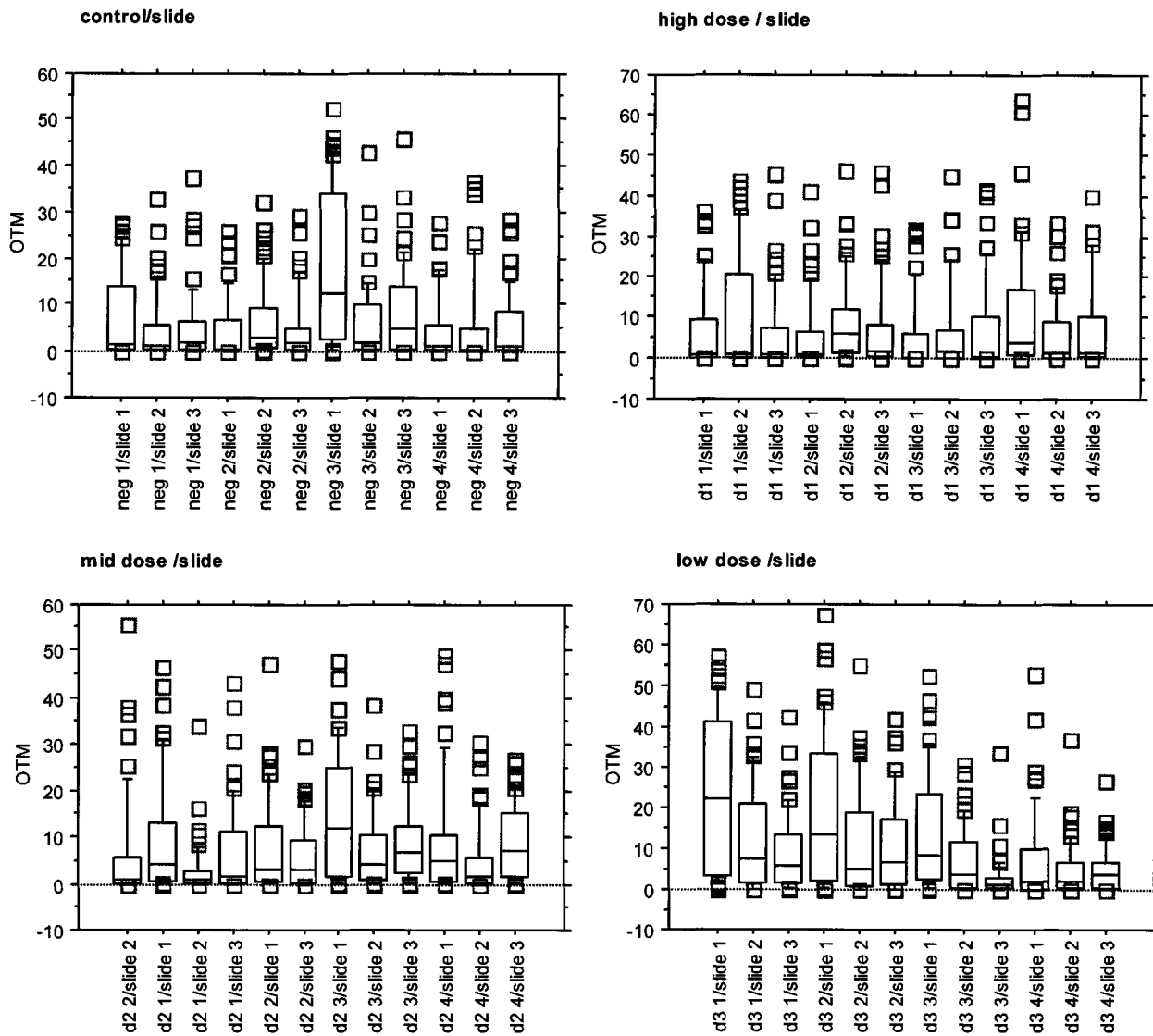
U	146812.500
U'	213187.500
Z value	-5.529
P value	<.0001
Corrected z for ex-aequo	-5.529
Corrected p for ex-aequo	< .0001
# ex-aequo	1

1649 omitted occurrences

	Number	Sum of Ranks	Mean of Ranks
3	600	327112.500	545.188
neg	600	393487.500	655.813

1649 omitted occurrences

## Appendix No. 5: Individual representation of distributions / Duodenum



High dose d1 : 400 mg/kg/day (x2)

Mid dose d2 : 200 mg/kg/day (x2)

Low dose d3 : 100 mg/kg/day (x2)

**Appendix No. 6: Non-parametric statistical analysis / Duodenum**☐ **F OF SNEDECOR: HOMOGENEITY BETWEEN GROUP VARIANCES / DUODENUM****F Test for OTM**

Total groups w/o positive control

	Variance ratio	Num DDL	Denom DDL	F	p
1, 2	1.194	599	599	1.194	.0301
1, 3	.717	599	599	.717	<.0001
1, neg	1.299	599	598	1.299	.0014
2, 3	.601	599	599	.601	<.0001
2, neg	1.088	599	598	1.088	.3042
3, neg	1.810	599	598	1.810	<.0001

**Group OTM**

Group Variable : total groups w/o positive control

	Number	Mean	Variance	Std Dev	Std Error
1	600	7.213	127.645	11.298	.461
2	600	7.744	106.892	10.339	.422
3	600	10.550	177.908	13.338	.545
neg	599	6.513	98.276	9.913	.405

☐ **KRUSKAL-WALLIS / DUODENUM**

DDL	3
# Groupes	4
# ex-aequo	2
H	65.392
P value	<.0001
Corrected H for ex-aequo	65.394
Corrected p for ex-aequo	<.0001

450 omitted occurrences

	Number	Sum of Ranks	Mean of Ranks
1	600	656294.000	1093.823
2	600	747237.000	1245.395
3	600	819944.000	1366.573
neg	599	655325.000	1094.032

450 omitted occurrences

☐ **MANN-WHITNEY / DUODENUM**

• **CONTROL vs. HIGH DOSE**

**Mann-Whitney U for OTM**  
control vs. high dose

U	179360.000
U'	180040.000
Z value	-0.57
P value	.9548
Corrected z for ex-aequo	-.057
Corrected p for ex-aequo	.9548
# ex-aequo	1

1650 omitted occurrences

	Number	Sum of Ranks	Mean of Ranks
1	600	359660.000	599.433
neg	599	359740.000	600.568

1650 omitted occurrences

• **CONTROL vs. MID DOSE**

**Mann-Whitney U for OTM**  
control vs. mid dose

U	156344.000
U'	203056.000
Z value	-3.896
P value	<.0001
Corrected Z for ex-aequo	-3.896
Corrected p for ex-aequo	<.0001
# ex-aequo	1

1650 omitted occurrences

	Number	Sum of Ranks	Mean of Ranks
2	600	383356.000	638.927
neg	599	336044.000	561.008

1650 omitted occurrences

- **CONTROL vs. LOW DOSE**

**Mann-Whitney U for OTM**  
**control vs. Low dose**

U	139241 000
U '	220159 000
Z value	-6.749
P value	<.0001
Corrected z for ex-aequo	-6 749
Corrected p for ex-aequo	< 0001
# ex-aequo	2

1650 omitted occurrences

	Number	Sum of Ranks	Mean of Ranks
3	600	400459.000	667.432
neg	599	318941.000	532.456

1650 omitted occurrences

## Appendix No. 7: Individual values for Nuclei's OTM / STOMACH

Test item: Dose	Distilled water		Organ	STOMACH		1 <sup>st</sup> treatment		2 <sup>nd</sup> treatment		25/09/2007			26/09/2007		
	0 ml/kg/day (x2)									65/14			65/11		
	Animal N°	Slide No. BC-07-13		File No. BC-07-13	No. of cal	Oliver's Moment	Oliver's Moment	Oliver's Moment	Oliver's Moment	Oliver's Moment	Oliver's Moment	Oliver's Moment	Oliver's Moment		
	213 A	213 B	213 C	214 A	214 B	214 C	215 A	215 B	215 C	216 A	216 B	216 C			
	Q1	Q2	Q3	Q1	Q2	Q3	E1	E2	E3	G1	G2	G3			
	Q1.xls	Q2.xls	Q3.xls	Q1.xls	Q2.xls	Q3.xls	E1.xls	E2.xls	E3.xls	G1.xls	G2.xls	G3.xls			
	Oliver's Moment												Oliver's Moment		
1	4.05	0.72	3.29	0.04	0.40	0.01	8.02	24.89	11.38	2.22	0.26	3.80			
2	13.34	0.35	32.78	3.20	2.35	8.81	2.55	1.36	0.28	17.67	22.45	0.14			
3	8.45	1.26	0.28	8.90	1.09	0.60	2.27	1.74	0.23	1.38	0.18	0.01			
4	2.32	0.01	1.54	0.57	0.09	1.83	6.83	21.04	1.69	0.34	16.31	16.28			
5	0.21	3.35	7.04	0.24	2.23	1.58	1.14	62.38	1.09	0.68	0.58	0.52			
6	6.14	2.23	21.62	2.85	6.57	0.11	33.20	63.05	9.57	1.97	0.54	1.92			
7	1.94	1.02	0.20	10.55	2.56	0.39	20.80	27.13	4.30	0.46	0.67	0.13			
8	0.58	0.17	9.17	2.26	2.08	1.11	13.37	26.35	1.38	0.14	23.15	6.32			
9	7.78	0.84	0.54	3.81	0.13	4.83	1.02	19.86	4.53	16.46	0.20	0.13			
10	12.47	0.33	3.59	1.80	1.40	0.16	7.15	22.09	0.40	10.91	0.11	5.37			
11	0.01	1.56	4.22	0.88	18.17	0.72	0.77	5.47	22.15	1.31	2.59	0.00			
12	0.90	0.32	3.10	7.79	24.68	1.37	0.67	0.12	0.20	2.47	19.44	12.58			
13	0.83	24.94	9.01	4.75	0.85	5.71	26.80	32.44	1.85	18.52	0.23	0.08			
14	3.12	15.02	0.72	2.88	0.16	0.76	2.97	22.67	0.35	26.07	0.38	23.42			
15	3.61	4.75	0.13	0.27	0.55	0.19	1.20	0.58	1.17	15.08	3.93	2.74			
16	1.57	3.98	0.16	1.67	0.47	5.11	20.86	40.36	0.51	0.10	14.75	15.70			
17	0.91	0.44	13.15	0.96	3.84	0.59	22.12	1.33	0.13	16.71	3.33	19.82			
18	3.30	0.05	2.04	3.33	1.30	0.59	51.62	13.60	18.61	0.18	0.81	0.03			
19	1.76	0.25	0.91	5.06	1.19	0.57	0.04	59.95	5.42	12.73	1.05	10.05			
20	1.72	0.25	0.91	0.10	0.14	0.02	9.74	29.73	2.27	19.90	6.79	3.04			
21	2.70	5.52	0.00	2.66	0.82	0.57	6.69	20.88	8.98	1.57	8.43	0.72			
22	0.88	0.21	2.90	0.43	0.19	0.00	55.34	16.53	26.08	2.90	2.02	5.20			
23	10.38	0.00	1.88	0.73	0.34	4.71	22.72	64.33	4.18	17.49	10.45	1.93			
24	1.17	2.45	4.81	1.56	4.29	0.34	4.84	2.32	37.24	16.82	8.48	3.88			
25	9.50	1.24	6.39	2.79	2.14	2.14	63.54	6.11	13.28	7.89	2.19	2.05			
26	15.94	1.51	4.31	5.58	3.88	1.44	10.49	12.05	3.33	0.16	5.32	2.46			
27	2.32	3.06	8.61	2.01	0.10	1.95	14.08	12.60	1.28	0.17	3.55	1.55			
28	1.86	0.44	3.39	3.65	2.21	2.06	19.98	0.64	0.77	11.36	0.01	14.35			
29	5.32	2.64	4.60	0.21	0.09	2.80	0.35	2.45	0.44	1.42	0.38	0.01			
30	0.33	1.38	0.76	11.64	0.50	0.77	9.85	55.72	8.75	36.25	1.85	0.06			
31	0.18	7.85	2.90	0.17	0.09	0.66	10.35	6.03	0.15	0.22	0.95	19.79			
32	1.52	0.09	0.44	1.38	1.51	0.02	2.16	9.36	18.12	16.09	0.79	0.22			
33	13.81	6.33	25.76	0.32	12.79	0.05	26.36	2.62	0.01	0.06	4.06	0.24			
34	1.54	0.32	1.34	5.70	0.68	0.14	7.56	7.22	11.98	0.57	2.96	0.64			
35	0.06	3.29	0.92	2.05	0.65	2.60	2.27	0.82	1.89	13.83	7.84	1.14			
36	0.02	0.03	4.28	2.64	12.17	4.79	5.79	35.07	3.01	7.50	15.31	4.84			
37	1.05	2.33	3.27	0.13	0.81	0.07	34.15	0.91	3.98	1.60	9.02	19.62			
38	3.25	0.48	3.81	2.33	3.21	11.82	34.42	33.13	16.81	39.60	0.05	8.16			
39	0.12	0.08	0.38	1.90	0.00	11.37	4.20	5.30	0.64	11.03	22.58	11.71			
40	10.06	0.58	4.25	3.45	0.18	0.11	47.35	10.90	0.18	0.01	0.08	18.13			
41	19.06	6.80	9.54	1.11	0.32	0.36	17.20	41.40	4.35	22.15	0.48	6.73			
42	2.91	0.05	6.65	0.70	0.01	1.77	26.19	54.86	0.77	1.23	0.11	13.63			
43	0.00	0.55	3.82	11.54	1.32	1.02	12.82	4.29	0.06	3.05	0.39	15.86			
44	0.60	3.84	2.61	3.94	0.01	0.19	47.63	50.48	0.27	18.09	1.36	0.39			
45	0.51	0.04	2.17	1.17	0.01	1.38	43.82	12.31	5.68	0.07	0.08	7.37			
46	0.75	1.52	1.15	6.30	0.53	1.09	20.28	0.15	12.78	15.81	9.19	9.99			
47	5.30	0.00	1.87	1.22	1.43	0.24	12.70	33.22	0.52	28.43	0.08	5.21			
48	1.27	6.98	0.42	0.32	3.74	2.74	37.82	26.84	10.10	10.27	0.68	8.97			
49	0.03	0.22	7.04	0.02	5.42	0.68	3.04	5.82	21.35	0.16	0.59	0.06			
50	0.66	0.52	2.28	0.08	4.79	0.67	68.99	21.24	20.91	1.26	0.93	12.24			
Median/slides	1.74	0.78	3.00	1.96	0.83	0.74	11.60	15.07	2.64	2.97	1.21	3.84			
Median/animal								8.86							
Median/dose		1.74			1.14		2.26				2.53				

Test item:		Catéchol			Organ.		STOMACH		1 <sup>st</sup> treatment:		25/09/2007		
Dose:		400 mg/kg/day (x2)							2 <sup>nd</sup> treatment:		26/09/2007		
Animal N°	Slide No. BC-07-Code BC-07-13	6518			6517			6520			6519		
		220 A	220 B	220 C	221 A	221 B	221 C	222 A	222 B	222 C	223 A	223 B	223 C
File No. BC-07-13		B1.xls	B2.xls	B3.xls	K1.xls	K2.xls	K3.xls	D1.xls	D2.xls	D3.xls	S1.xls	S2.xls	S3.xls
No. of cell		Olive tailMoment			Olive tailMoment			Olive tailMoment			Olive tailMoment		
1		0.40	0.06	1.14	0.18	32.68	0.12	21.16	19.04	0.00	0.05	6.61	0.31
2		1.81	0.02	4.54	0.37	0.36	0.66	2.38	0.57	30.05	0.00	0.18	3.27
3		50.88	1.30	11.26	0.01	0.35	0.42	0.53	0.88	0.12	0.01	2.60	2.02
4		0.14	0.03	4.87	13.43	1.08	0.16	0.34	7.54	0.45	0.10	0.07	0.16
5		0.45	29.35	0.14	0.26	0.10	0.02	33.95	1.32	1.10	0.01	0.64	0.66
6		0.02	12.28	0.14	0.24	0.01	1.25	2.24	0.49	3.83	0.43	5.63	0.32
7		9.73	0.07	36.81	4.59	0.01	6.52	0.66	42.96	2.95	0.01	0.02	0.13
8		0.06	33.20	17.45	0.00	5.47	0.01	39.65	1.13	1.52	0.01	0.11	0.07
9		27.51	0.76	5.43	0.30	0.18	5.14	0.26	27.52	0.22	0.01	0.66	0.05
10		6.84	0.01	0.90	0.13	0.84	0.24	46.22	0.15	0.15	2.16	0.11	3.34
11		0.27	6.40	35.42	0.03	1.18	0.49	0.30	21.59	0.01	0.00	0.01	19.90
12		33.28	46.74	2.16	0.06	0.25	0.02	52.37	1.64	2.24	0.02	1.85	1.23
13		1.39	16.73	0.87	0.01	43.19	2.30	9.03	30.53	0.01	0.00	0.47	0.01
14		49.56	0.15	2.14	0.00	0.08	0.16	2.64	6.60	1.72	2.67	0.02	0.93
15		49.90	2.25	0.51	0.22	0.08	0.03	0.96	0.05	0.05	0.72	0.01	0.10
16		39.31	0.17	0.23	0.12	0.04	0.01	43.31	1.02	0.00	0.00	5.29	0.02
17		14.13	0.36	34.98	0.72	0.39	0.03	0.06	1.04	39.77	0.02	0.16	0.32
18		54.30	6.54	0.03	0.00	0.67	0.17	1.71	1.57	2.22	0.08	0.00	0.43
19		3.28	4.32	0.50	1.10	1.61	0.00	10.66	22.40	24.25	0.00	3.37	1.73
20		7.10	0.05	0.02	0.73	12.63	0.06	7.52	0.50	0.01	8.25	0.09	0.01
21		1.95	0.62	6.51	0.11	11.31	2.54	24.78	2.63	3.30	0.16	0.00	0.07
22		6.50	7.39	14.55	38.70	0.03	0.02	0.59	0.01	18.33	0.54	0.00	0.01
23		2.02	9.68	1.21	0.05	2.54	2.35	3.84	3.88	0.11	0.50	0.03	0.06
24		0.07	10.05	5.96	0.06	0.65	0.12	0.62	0.35	0.00	0.85	0.03	0.03
25		6.54	9.66	0.94	0.31	0.14	0.66	0.86	19.29	13.97	1.45	0.38	0.02
26		0.56	18.37	1.00	0.16	63.85	69.58	5.51	1.28	0.05	0.69	0.39	0.43
27		4.95	24.22	0.02	0.20	0.11	0.13	25.08	19.54	0.07	0.34	0.00	0.00
28		0.30	1.81	31.49	0.15	0.11	0.17	35.89	0.03	0.01	0.05	0.24	0.44
29		7.78	1.30	43.83	0.90	0.09	19.62	56.07	2.12	0.51	0.42	0.05	0.24
30		39.39	1.44	45.36	0.12	2.33	15.06	0.36	14.41	0.21	0.02	1.54	1.34
31		5.48	9.75	4.53	0.73	0.27	1.71	12.10	12.13	8.57	0.03	0.01	0.34
32		21.76	7.85	6.48	0.38	1.34	0.33	1.11	5.17	3.32	1.10	0.48	0.04
33		13.65	0.47	2.21	0.69	0.03	8.59	1.40	22.14	2.96	0.07	0.01	0.20
34		0.45	0.13	46.70	0.34	1.60	35.39	0.15	0.19	11.57	0.01	0.37	29.37
35		0.58	2.32	6.88	1.55	0.06	2.04	1.55	3.76	5.23	0.39	0.00	0.06
36		9.04	31.09	0.16	0.90	0.14	0.02	11.76	3.40	30.79	0.06	1.27	0.01
37		10.21	35.91	0.07	7.06	1.33	0.23	10.60	3.68	15.20	0.02	0.77	0.07
38		31.75	68.20	11.77	12.80	2.33	0.50	6.44	29.01	0.64	0.14	0.77	0.05
39		3.73	37.59	25.68	0.76	1.22	2.27	0.46	5.27	11.12	0.13	0.62	0.02
40		20.83	2.01	74.65	1.87	0.96	0.05	33.85	1.93	9.09	0.74	0.71	0.03
41		0.14	18.56	56.94	2.24	2.39	4.29	2.98	9.02	0.34	0.01	0.14	4.98
42		6.51	27.14	50.91	0.14	2.97	0.47	11.40	0.15	0.00	0.37	0.11	0.10
43		0.32	6.81	36.92	0.44	4.13	0.00	9.10	24.80	0.02	3.26	0.17	0.15
44		5.00	6.19	0.49	0.49	0.76	0.01	0.22	0.88	3.62	0.05	0.39	0.24
45		0.37	0.04	3.04	0.59	2.77	0.37	50.39	0.02	0.24	0.01	0.11	0.07
46		7.71	0.14	65.88	8.77	17.16	0.01	0.16	17.89	16.68	0.01	0.16	0.00
47		37.40	20.62	3.31	0.21	1.22	1.11	32.34	1.53	25.11	2.39	0.06	0.01
48		5.09	3.94	2.93	8.63	3.18	0.00	1.29	0.26	3.76	6.98	0.13	0.06
49		63.59	12.03	31.52	49.85	3.67	0.92	62.91	8.96	0.07	0.00	0.26	0.06
50		5.10	18.30	31.62	72.06	0.08	10.86	45.24	15.10	0.22	0.28	3.86	10.72
Median/slide		5.99	6.29	4.70	0.36	0.90	0.40	4.67	3.02	1.31	0.08	0.16	0.14
Median/animal			5.45			0.45			2.51			0.13	
													0.31

Test Item Dose:	Catéchol 200 mg/kg/day (x2)	Organ	STOMACH	1 <sup>st</sup> treatment: 2 <sup>nd</sup> treatment		25/09/2007 26/09/2007						
				6521			6522			6525		
				224 A	224 B	224 C	225 A	225 B	225 C	226 A	226 B	226 C
Animal N°	J1.xls	J2.xls	J3.xls	C1.xls	C2.xls	C3.xls	L1.xls	L2.xls	L3.xls	R1.xls	R2.xls	R3.xls
Slide No. BC-07- Code BC-07-13	J1	J2	J3	C1	C2	C3	L1	L2	L3	R1	R2	R3
File No. BC-07-13	J1.xls	J2.xls	J3.xls	C1.xls	C2.xls	C3.xls	L1.xls	L2.xls	L3.xls	R1.xls	R2.xls	R3.xls
No. of cell	Olive tailMoment			Olive tailMoment			Olive tailMoment			Olive tailMoment		
1	0.00	9.37	0.20	0.01	0.79	0.04	9.71	5.03	0.23	0.00	1.30	2.14
2	14.41	0.01	0.04	0.03	0.13	0.45	16.47	0.14	0.07	0.01	0.00	4.42
3	1.70	0.58	0.03	0.18	0.02	0.03	0.59	2.66	0.10	4.35	0.69	19.34
4	6.71	0.05	0.01	0.02	1.20	0.53	7.33	0.02	0.19	15.89	1.01	1.86
5	0.35	0.06	0.45	0.19	0.19	1.69	0.31	22.21	0.90	0.00	4.46	17.84
6	0.21	0.18	0.03	1.99	0.35	0.09	1.66	2.27	6.22	0.26	0.07	0.05
7	0.00	0.18	2.25	6.21	0.00	1.62	0.18	0.04	0.71	1.04	0.01	3.41
8	1.24	0.03	4.31	0.00	0.05	0.89	0.29	0.00	1.55	0.21	0.15	3.29
9	2.14	0.33	0.01	0.13	11.00	0.00	1.72	2.43	1.24	0.59	0.08	0.29
10	0.74	0.34	31.84	0.95	5.58	0.24	0.45	1.11	0.52	0.13	0.63	0.00
11	0.87	2.06	0.16	0.12	0.01	0.00	2.78	0.34	0.10	32.04	0.03	0.00
12	0.28	6.27	0.09	0.01	0.17	0.04	0.70	0.70	0.23	0.24	0.61	2.67
13	0.00	0.09	0.01	0.00	0.01	0.06	0.27	0.82	9.76	6.41	0.44	15.21
14	0.76	0.58	0.00	0.12	0.00	0.17	6.00	2.18	6.09	0.00	0.85	0.41
15	1.63	3.78	0.23	28.25	0.00	0.01	5.86	19.48	0.33	0.02	0.77	4.29
16	1.36	1.46	0.00	0.10	1.16	0.61	0.08	1.19	0.55	0.00	0.03	0.14
17	6.28	0.22	8.41	0.60	0.00	0.00	0.03	0.47	0.08	0.02	0.22	0.09
18	0.06	0.10	1.41	1.52	0.41	0.03	3.54	5.68	0.11	0.19	0.32	1.35
19	0.11	0.02	0.00	0.01	0.27	7.30	0.05	0.02	0.44	2.11	0.12	0.00
20	0.02	38.65	1.28	0.61	1.64	0.52	0.00	0.12	6.15	0.03	0.05	0.08
21	0.00	12.16	0.19	0.52	0.00	0.24	0.00	4.35	17.75	2.97	24.99	1.16
22	0.29	0.18	0.41	0.01	0.02	0.00	22.16	2.02	0.31	0.00	0.02	8.94
23	0.05	0.53	0.35	0.02	5.69	0.00	5.06	0.35	13.76	1.17	0.19	21.37
24	0.01	0.32	0.00	11.54	2.01	1.81	3.12	1.61	0.64	16.74	0.71	0.09
25	1.44	0.13	0.26	0.08	0.16	1.89	2.01	4.46	13.06	1.81	12.77	4.07
26	0.01	0.45	0.75	0.01	0.01	0.83	3.71	0.21	0.01	0.34	1.93	1.36
27	0.15	0.11	0.03	0.02	0.01	1.56	0.27	16.24	1.29	0.00	0.11	0.00
28	0.10	0.26	0.01	0.00	0.01	2.19	2.19	0.47	9.62	0.00	0.00	4.77
29	0.22	1.29	1.81	0.00	0.08	3.78	0.82	4.18	0.01	0.46	0.74	21.29
30	0.01	0.29	0.84	0.10	0.23	3.36	2.89	1.08	32.89	3.11	0.00	1.06
31	0.20	0.09	5.39	0.00	0.43	1.14	4.20	0.23	0.18	0.00	0.70	1.99
32	0.02	0.00	0.13	0.00	0.05	0.00	3.32	1.27	0.08	5.77	0.00	1.99
33	0.00	0.03	0.33	0.00	0.00	0.88	0.04	0.00	9.67	2.47	12.99	0.30
34	0.37	0.01	10.07	0.83	1.46	1.20	23.84	11.76	3.31	0.00	0.30	0.38
35	0.00	0.88	1.80	0.03	0.06	1.43	26.50	5.64	0.49	3.07	0.97	4.83
36	0.04	0.12	0.44	0.13	0.81	0.49	0.00	0.00	0.67	0.52	13.72	0.11
37	0.27	0.14	0.08	0.22	0.30	0.05	9.40	0.43	1.11	3.81	0.03	0.09
38	0.74	0.03	18.57	0.76	0.00	0.00	18.68	0.08	26.42	0.33	6.11	1.01
39	0.01	7.37	0.00	2.82	1.54	0.02	0.12	1.89	4.25	4.98	0.31	0.27
40	5.83	0.04	0.07	0.50	0.68	0.02	4.07	8.24	1.11	4.38	0.07	0.00
41	0.16	0.26	1.01	0.01	26.80	0.45	0.63	0.13	0.15	0.16	0.37	0.56
42	4.76	0.70	0.63	0.04	0.00	0.06	0.96	15.76	0.36	2.52	0.07	2.32
43	0.17	0.01	0.72	0.04	0.02	6.49	0.51	0.26	0.38	1.16	0.17	0.00
44	0.17	0.01	0.03	0.09	2.02	0.60	1.29	0.17	0.34	0.71	0.77	1.79
45	0.00	0.02	0.76	0.30	0.25	0.00	1.38	0.01	0.17	0.86	0.01	0.01
46	0.11	0.12	0.19	0.31	0.54	3.57	0.01	2.78	0.29	0.26	8.64	0.05
47	11.02	0.03	0.47	0.43	0.01	0.77	22.04	0.37	0.00	0.96	4.81	0.00
48	2.61	0.01	42.34	0.01	0.13	1.05	0.00	0.00	0.79	1.01	0.53	4.87
49	11.65	0.00	0.00	0.71	5.85	4.39	6.23	21.28	7.36	0.86	0.00	1.06
50	0.04	0.44	0.79	0.07	0.23	0.28	0.02	1.16	6.41	0.96	0.00	0.02
Median/slide	0.20	0.18	0.30	0.10	0.18	0.47	1.52	1.10	0.60	0.65	0.41	1.06
Median/animal	0.21			0.18			0.80			0.60		
Median/dose				0.35								

Test item Dose	Organ	STOMACH		1 <sup>st</sup> treatment 2 <sup>nd</sup> treatment		25/09/2007 26/09/2007											
		Animal N°	Slide No. BC-07-13	File No. BC-07-13	No. of cell	228 A	228 B	228 C	229 A	229 B	229 C	230 A	230 B	230 C	231 A	231 B	231 C
		Catéchol 100 mg/kg/day (x2)		6527		6529		6526		6530							
		Olive tailMoment		Olive tailMoment		Olive tailMoment		Olive tailMoment		Olive tailMoment		Olive tailMoment		Olive tailMoment		Olive tailMoment	
		11.xls	12.xls	13.xls	P1.xls	P2.xls	P3.xls	M1.xls	M2.xls	M3.xls	H1.xls	H2.xls	H3.xls				
1		0.51	0.01	6.01	0.12	10.26	19.28	0.35	2.07	0.45	1.30	0.89	0.10				
2		0.00	0.46	4.86	2.83	10.26	1.83	5.31	0.61	1.85	0.49	17.90	0.33				
3		1.95	1.38	0.02	1.39	3.39	0.42	6.39	0.23	0.05	1.21	4.24	0.31				
4		1.48	3.33	0.40	3.05	4.00	3.40	1.60	0.29	0.41	1.15	0.58	0.62				
5		1.46	0.82	2.03	0.00	4.58	0.23	0.86	0.00	1.70	1.03	4.25	1.68				
6		21.82	1.47	0.11	0.33	0.44	0.04	0.24	0.20	6.44	2.02	16.29	10.51				
7		0.14	3.51	0.00	0.70	23.09	1.09	0.31	0.29	0.92	0.67	2.79	2.38				
8		0.64	0.02	1.07	0.57	0.92	17.00	0.36	1.98	0.09	2.74	2.19	0.44				
9		0.09	0.08	0.47	0.48	10.12	0.83	1.14	2.30	17.25	0.34	0.42	1.27				
10		0.73	0.04	4.30	0.56	6.06	0.43	12.39	0.38	4.79	0.17	10.43	1.87				
11		0.88	0.10	0.36	0.13	5.54	2.57	0.69	0.84	16.50	0.12	0.35	7.83				
12		1.19	1.83	0.32	5.21	0.91	0.06	4.41	1.53	3.43	9.23	0.16	9.21				
13		0.28	18.33	9.14	1.32	0.28	0.45	2.24	1.07	0.01	2.29	0.66	17.11				
14		1.59	3.13	0.22	2.16	0.82	4.08	10.43	6.57	0.63	0.01	0.27	0.06				
15		0.99	0.00	15.90	0.05	15.26	0.25	0.65	0.32	23.51	14.16	0.10	20.67				
16		6.61	3.47	1.59	1.42	13.45	0.01	0.01	14.47	0.00	3.65	0.71	0.47				
17		1.98	0.54	1.19	0.16	1.79	0.43	6.77	0.43	0.00	3.28	12.82	2.14				
18		0.47	0.77	0.40	0.04	3.55	3.53	4.66	0.39	20.47	0.59	0.12	0.08				
19		4.41	4.13	2.41	0.54	0.66	0.22	0.21	1.17	16.72	0.53	0.06	25.01				
20		0.07	21.14	0.01	3.01	12.03	0.86	11.61	0.02	0.04	0.85	0.15	0.01				
21		20.55	12.28	1.01	0.20	0.41	2.62	2.85	0.38	0.04	2.30	1.25	6.85				
22		0.60	0.31	30.19	0.07	1.50	40.93	3.65	2.26	0.23	4.00	1.70	1.13				
23		1.15	1.29	34.68	9.07	2.66	0.94	0.16	1.48	2.66	0.88	10.32	1.24				
24		0.59	0.08	0.94	0.46	1.62	3.14	0.95	0.24	2.81	0.01	11.84	1.13				
25		0.06	0.48	5.04	0.24	1.70	0.13	4.85	1.42	4.40	0.18	0.10	0.66				
26		0.03	4.81	0.52	0.37	3.70	0.39	5.03	0.42	9.73	0.29	0.95	2.19				
27		1.81	1.82	0.50	4.80	0.74	1.48	11.31	0.51	0.90	2.39	1.17	0.00				
28		0.93	3.42	1.21	8.48	0.73	1.92	0.78	0.01	14.59	2.19	0.74	7.20				
29		0.17	0.28	0.17	1.10	4.32	7.52	0.29	16.40	1.70	0.01	3.18	20.34				
30		3.48	0.05	0.22	0.07	0.54	0.44	31.80	0.00	0.52	6.13	0.17	1.94				
31		1.92	0.42	0.51	0.26	2.80	1.92	9.84	0.22	17.07	0.00	0.70	0.26				
32		0.48	4.72	0.06	0.25	8.07	1.71	0.53	6.12	1.74	0.15	8.35	1.60				
33		0.01	3.29	0.04	0.90	6.88	0.52	2.05	0.02	0.08	13.61	3.77	0.28				
34		9.15	0.17	1.06	2.64	1.94	1.58	0.13	0.01	0.35	28.93	2.78	0.28				
35		0.73	1.58	4.71	17.34	11.36	21.94	0.11	0.07	4.08	0.84	0.00	2.60				
36		0.83	1.06	10.63	15.11	4.94	1.91	0.67	0.27	2.18	0.54	0.70	8.69				
37		0.73	1.56	0.29	3.02	38.26	26.27	13.82	4.04	1.38	0.09	0.23	0.07				
38		12.10	0.04	0.92	1.87	7.29	18.83	1.00	0.07	0.06	9.62	1.98	19.07				
39		11.92	37.88	0.92	0.50	2.14	1.12	0.02	3.86	0.24	3.00	0.76	1.35				
40		8.34	0.17	0.09	2.08	42.57	43.29	2.16	1.07	1.53	0.13	1.36	14.29				
41		1.45	0.34	4.80	0.25	1.33	0.74	15.94	7.70	0.36	0.68	0.08	8.53				
42		0.23	2.80	0.01	23.19	10.07	0.67	0.34	1.67	2.67	3.75	0.47	1.39				
43		0.19	1.52	10.23	1.16	3.93	2.68	0.01	1.83	2.87	45.76	0.45	1.83				
44		1.08	3.88	6.52	10.32	0.09	0.13	3.04	0.23	25.19	0.12	3.37	0.96				
45		0.22	1.05	0.42	0.16	17.85	0.18	0.00	1.04	23.16	6.04	0.15	6.99				
46		3.62	1.61	3.54	2.08	0.28	26.45	0.00	0.38	0.18	1.76	4.76	1.01				
47		1.68	0.70	2.38	0.36	1.03	2.65	5.99	0.69	0.17	0.17	0.03	3.15				
48		0.56	0.17	0.51	0.27	0.55	6.58	2.11	9.23	23.63	1.31	3.13	8.65				
49		0.64	4.39	0.55	3.02	0.56	8.69	8.62	0.93	8.90	1.45	0.20	5.18				
50		0.42	1.12	2.07	0.81	2.17	14.17	1.92	0.34	0.57	21.30	1.83	3.37				
Median/slide		0.86	1.20	0.93	0.76	2.41	1.53	1.76	0.56	1.61	1.18	0.75	1.76				
Median/animal			0.96			1.49			1.02			1.26					
Median/dose																	

Test item:		Methylnitronitrosoguanidine 20 mg/kg/day (x1)				Organ Treatment				STOMACH 26/09/2007			
Dose		6534				6532				6531			
Animal N°		217 A	217 B	217 C		218 A	218 B	218 C		219 A	219 B	219 C	
Slide No. BC-07-13	A1	A1.xls	A2.xls	A3.xls		F1.xls	F2.xls	F3.xls		N1.xls	N2.xls	N3.xls	
File No. BC-07-13	A1.xls	A2.xls	A3.xls			F1.xls	F2.xls	F3.xls		N1.xls	N2.xls	N3.xls	
No. of cell													
1		13.89	27.00	8.97		34.38	42.87	10.55		0.76	9.98	0.20	
2		39.76	2.38	20.01		14.11	0.26	11.25		1.79	6.78	0.37	
3		86.15	28.26	1.00		2.64	0.65	43.38		1.51	4.59	0.11	
4		75.45	2.18	61.77		0.29	43.44	25.43		0.85	2.04	4.31	
5		39.16	36.80	28.03		20.63	19.06	2.67		0.99	3.54	6.80	
6		15.76	19.01	41.72		17.37	0.02	0.79		0.94	4.75	0.03	
7		22.63	7.24	21.56		19.69	11.33	3.38		5.55	1.22	0.96	
8		0.35	6.79	30.17		43.81	9.48	2.99		1.97	0.90	3.74	
9		3.35	60.71	22.98		1.39	3.96	1.80		1.44	0.95	1.39	
10		4.19	33.88	46.57		6.86	9.30	15.72		1.45	4.28	0.16	
11		79.27	52.00	0.09		0.65	30.00	5.76		0.19	0.62	8.16	
12		26.83	64.66	2.33		26.79	5.89	34.89		0.79	0.72	3.64	
13		41.24	25.33	56.79		4.76	0.57	39.44		1.74	0.71	0.67	
14		5.76	8.47	65.79		32.42	16.47	12.87		4.11	0.02	0.85	
15		0.02	55.74	5.32		0.42	2.32	83.01		0.01	0.11	0.29	
16		4.12	73.82	54.01		3.60	30.39	45.39		4.00	0.00	2.41	
17		13.92	26.12	58.36		0.41	3.33	55.08		3.09	2.86	0.24	
18		41.86	23.08	82.75		16.91	19.23	37.48		0.23	3.41	0.00	
19		7.71	48.88	21.35		36.29	1.03	0.26		8.29	1.49	0.05	
20		47.56	42.36	26.57		10.03	5.10	12.10		10.09	0.03	0.50	
21		62.94	25.67	11.62		4.00	0.34	4.15		0.00	0.81	0.99	
22		38.68	33.62	1.76		52.73	5.93	76.19		5.31	9.28	6.54	
23		0.00	48.34	33.22		0.02	53.81	45.16		0.20	0.05	0.51	
24		7.27	24.45	15.23		4.12	11.75	23.69		1.49	1.22	0.00	
25		44.01	6.42	0.90		39.62	1.96	4.23		10.46	0.27	0.47	
26		7.23	73.51	33.61		0.04	40.05	0.66		1.11	1.33	3.21	
27		3.44	0.43	50.32		0.09	0.89	5.45		0.60	0.04	0.42	
28		35.56	13.27	3.19		28.87	11.85	0.54		0.14	1.24	0.01	
29		6.45	31.01	39.28		0.22	12.22	16.38		0.02	0.74	0.47	
30		46.37	27.48	72.40		0.02	32.23	56.14		5.60	7.18	4.35	
31		75.49	0.09	95.74		17.13	4.51	3.43		24.76	0.47	0.47	
32		53.50	65.48	44.47		9.25	5.11	23.14		17.18	3.60	0.49	
33		66.53	48.56	80.86		12.56	1.34	0.25		3.80	4.01	6.82	
34		56.16	38.74	47.84		0.39	0.51	1.51		0.03	0.08	6.16	
35		2.86	10.19	0.05		37.98	46.16	20.73		0.76	2.50	0.19	
36		5.87	42.80	2.81		2.28	11.00	29.83		0.29	1.59	1.74	
37		5.71	0.36	59.68		0.48	0.00	35.66		1.85	0.83	5.77	
38		0.97	8.11	1.83		2.09	0.39	0.11		2.48	8.65	2.45	
39		9.96	17.01	10.89		5.78	2.14	58.26		2.03	0.05	1.15	
40		38.03	6.70	0.57		3.75	61.19	66.39		0.98	0.03	3.00	
41		64.85	5.80	11.37		3.41	41.19	43.35		0.65	0.29	3.92	
42		3.38	1.98	14.38		2.85	24.70	6.91		0.16	2.41	1.06	
43		3.23	2.92	37.42		3.72	0.22	24.31		0.53	0.61	8.14	
44		51.20	4.90	18.72		35.33	7.38	2.58		0.37	1.86	7.34	
45		47.57	20.42	47.84		11.49	15.88	19.06		1.89	4.53	0.05	
46		36.07	23.27	18.03		61.43	1.00	20.86		0.22	0.17	0.00	
47		27.86	9.29	36.82		0.20	17.28	22.28		0.54	2.00	0.25	
48		4.27	48.09	60.47		0.58	37.61	5.60		14.68	2.95	4.58	
49		15.10	34.15	3.20		50.84	2.46	0.28		0.05	0.05	3.26	
50		52.82	3.11	3.90		1.87	5.72	18.03		2.02	0.95	10.03	
Median/slide		24.73	24.89	24.77		5.09	6.65	16.05		1.27	1.22	0.98	
Median/animal			24.89				5.37				1.08		
Median/dose							5.37						

## Appendix No. 8: Individual values for Tail length / STOMACH

Test item:		Distilled water		Organ:		STOMACH		1 <sup>st</sup> treatment.		25/09/2007		26/09/2007	
Dose		0 mg/kg/day (x2)											
Animal N°	Slide No. BC-07-13 File No. BC-07-13	6512		6514		6511		6515					
		213 A	213 B	213 C	214 A	214 B	214 C	215 A	215 B	215 C	216 A	216 B	216 C
Q1.xls		Q2.xls	Q3.xls	Q1.xls	Q2.xls	Q3.xls	E1.xls	E2.xls	E3.xls	G1.xls	G2.xls	G3.xls	
tail length		tail length		tail length		tail length		tail length		tail length		tail length	
1		61.56	19.52	105.10	15.52	33.03	32.28	98.09	102.10	96.85	65.31	36.79	57.06
2		90.09	29.28	228.22	63.81	57.81	93.09	78.08	55.55	34.53	67.57	81.83	34.53
3		104.35	34.53	35.28	92.34	19.52	57.81	78.08	66.06	48.80	66.06	18.02	21.02
4		29.28	21.02	61.56	43.54	22.52	51.05	84.83	120.87	50.30	24.02	63.81	55.55
5		33.78	40.54	117.87	48.05	48.05	30.03	63.06	129.13	49.55	33.78	32.28	33.03
6		95.34	57.06	95.34	109.61	81.83	30.78	132.13	198.95	124.62	71.32	30.78	25.53
7		69.07	45.04	35.28	111.11	52.55	35.28	97.60	130.63	97.09	41.29	33.78	24.77
8		36.79	13.51	45.79	57.06	58.31	45.04	88.59	138.14	57.06	25.53	97.60	64.56
9		99.85	34.53	30.03	89.34	28.53	69.82	54.05	82.58	95.34	129.13	42.04	24.02
10		136.63	41.29	40.54	63.06	35.29	29.28	93.84	102.85	32.28	62.31	24.02	54.80
11		12.01	51.05	72.07	26.28	96.09	48.05	29.28	68.32	153.15	34.53	53.30	16.52
12		38.29	33.78	58.56	45.79	66.82	36.79	33.78	29.28	30.03	38.29	58.56	86.33
13		32.28	171.17	79.58	69.82	28.53	85.58	89.34	135.13	81.83	105.85	28.53	27.78
14		66.06	147.90	31.53	43.54	35.28	50.30	63.06	123.12	27.78	79.58	29.28	132.88
15		46.55	85.58	21.77	27.07	24.77	17.27	72.07	25.53	18.02	55.55	52.55	67.57
16		42.04	54.05	18.77	52.55	36.29	94.59	132.13	130.63	36.04	40.54	63.81	101.35
17		27.78	30.03	81.83	26.28	87.84	33.78	108.86	45.04	33.03	98.35	41.29	117.87
18		42.79	30.78	72.07	51.05	42.04	39.04	164.41	93.84	164.41	29.28	27.78	13.51
19		35.28	19.52	39.04	75.82	57.81	27.78	21.02	147.14	67.57	102.10	57.81	117.12
20		42.04	29.28	54.05	12.76	43.54	21.02	123.87	121.62	84.08	95.34	80.33	88.59
21		57.06	101.35	9.76	58.31	47.30	47.30	57.81	172.67	98.35	46.55	87.84	42.79
22		21.77	30.78	82.58	33.78	46.55	15.01	134.38	94.59	151.65	32.28	36.04	29.28
23		105.85	12.76	41.29	32.28	39.04	66.06	106.60	250.75	36.79	102.10	46.55	54.80
24		58.56	49.55	44.29	50.30	93.09	38.29	77.33	62.31	212.46	93.84	73.57	69.07
25		108.11	36.04	69.07	41.29	39.79	76.58	158.41	77.33	142.64	98.35	65.31	38.29
26		48.05	40.54	51.80	56.31	76.58	46.55	97.60	113.36	78.83	27.03	66.06	30.03
27		75.07	70.57	78.83	44.29	19.52	65.31	102.85	115.61	42.04	17.27	47.30	35.28
28		69.07	52.55	80.33	63.06	70.57	68.32	118.82	29.28	31.53	122.37	21.77	82.58
29		57.81	43.54	82.58	38.04	33.78	54.80	33.78	72.82	20.27	48.80	21.02	29.28
30		56.31	32.28	38.29	103.60	55.55	84.83	70.57	137.38	96.85	111.86	22.52	12.76
31		44.29	78.83	68.32	37.54	19.52	49.55	86.33	51.05	15.77	25.53	29.28	117.87
32		33.78	30.03	68.32	54.80	63.06	27.03	30.03	115.61	129.13	108.86	24.02	23.27
33		98.35	83.33	144.14	33.03	120.12	20.27	120.87	73.57	28.53	10.51	37.54	31.53
34		50.30	34.53	38.29	61.56	34.53	26.28	111.11	83.33	100.60	39.79	33.78	19.52
35		24.02	51.80	40.54	76.58	49.55	74.32	69.07	34.53	59.31	92.34	37.54	66.82
36		18.77	21.77	79.58	66.82	123.87	63.06	76.83	129.88	68.32	94.59	63.81	63.81
37		48.05	36.04	53.30	51.80	71.32	27.03	129.13	35.28	62.31	28.53	60.81	120.12
38		79.58	42.79	77.33	78.08	83.33	97.60	92.34	155.40	133.63	131.38	30.03	95.34
39		45.79	31.53	27.78	84.08	12.01	99.85	80.33	83.33	54.80	97.60	90.09	173.42
40		75.82	25.53	92.34	51.80	41.29	34.53	126.87	96.09	33.03	10.51	29.28	93.09
41		115.61	60.81	92.34	78.08	30.78	35.28	83.33	236.48	96.31	138.14	26.28	27.76
42		66.82	20.27	77.33	114.86	15.01	50.30	140.39	136.63	66.32	66.82	21.77	73.57
43		21.77	40.54	75.07	114.86	65.31	50.30	157.85	85.58	24.02	51.05	42.04	175.67
44		37.54	44.29	34.53	81.83	19.52	47.30	157.85	143.39	21.02	108.86	58.56	26.28
45		39.04	33.78	35.28	36.04	19.52	37.54	121.62	105.85	82.58	33.03	27.78	75.07
46		26.28	48.05	47.30	133.63	32.28	51.80	161.41	31.53	124.62	94.59	94.59	108.11
47		52.55	25.53	57.81	45.79	67.57	24.02	153.15	117.12	23.27	108.86	30.03	67.57
48		33.03	57.81	30.78	28.53	83.33	78.08	133.63	114.86	131.38	66.82	34.53	101.35
49		29.28	30.78	93.84	19.52	100.60	45.04	54.05	79.58	144.89	35.28	35.28	28.53
50		17.27	33.78	48.80	31.53	93.09	59.31	192.19	114.11	155.40	41.29	36.79	76.58
Mean/slide		55.16	45.82	63.24	56.55	52.84	49.80	97.64	103.92	76.08	67.04	45.72	63.08
Mean/animal		55.16	45.82	63.24	56.55	52.84	49.80	97.64	103.92	76.08	67.04	45.72	63.08
Mean/dose		55.16	45.82	63.24	56.55	52.84	49.80	97.64	103.92	76.08	67.04	45.72	63.08

## FSR-IPL 070402 / CATECHOL / RHODIA

Test item.	Catéchol 400 mg/kg/day (x2)	Organ	STOMACH	1 <sup>st</sup> treatment		25/09/2007		26/09/2007		223 A	223 B	223 C	223 A	223 B	223 C
				6517		6520		6519							
				221 A	221 B	221 C	222 A	222 B	222 C						
Animal N°	B1	B2	B3	K1	K2	K3	D1	D2	D3	S1	S2	S3	S1	S2	S3
Slide No. BC-07-13	B1.xls	B2.xls	B3.xls	K1.xls	K2.xls	K3.xls	D1.xls	D2.xls	D3.xls	S1.xls	S2.xls	S3.xls	S1.xls	S2.xls	S3.xls
File No. BC-07-13	B1.xls	B2.xls	B3.xls	K1.xls	K2.xls	K3.xls	D1.xls	D2.xls	D3.xls	S1.xls	S2.xls	S3.xls	S1.xls	S2.xls	S3.xls
No. of cell	tail length			tail length			tail length			tail length			tail length		
1	26.28	34.53	32.28	15.01	146.39	16.52	130.63	96.09	11.26	19.52	57.81	54.05	19.52	57.81	54.05
2	93.09	27.03	96.09	18.77	23.27	51.05	98.35	31.53	133.63	26.28	24.77	45.04	26.28	24.77	45.04
3	221.47	54.80	136.63	14.26	32.28	45.79	33.03	45.79	30.78	18.77	60.81	54.05	18.77	60.81	54.05
4	25.53	27.78	61.56	102.85	48.80	30.03	18.77	69.82	61.56	27.78	27.78	31.53	27.78	27.78	31.53
5	45.04	113.36	27.03	43.54	17.27	24.77	117.12	36.79	55.55	25.53	16.52	42.04	25.53	16.52	42.04
6	27.03	94.59	12.01	39.04	20.27	57.06	109.61	24.77	36.04	32.28	51.05	33.03	32.28	51.05	33.03
7	56.31	27.03	147.90	84.83	30.03	87.84	18.77	119.37	45.04	15.01	12.01	29.28	15.01	12.01	29.28
8	27.78	81.59	114.86	13.51	72.07	21.77	153.90	31.53	36.79	28.53	25.53	35.28	28.53	25.53	35.28
9	73.57	48.05	82.58	26.28	20.27	84.83	23.27	114.11	33.78	31.53	31.53	29.28	31.53	29.28	31.53
10	99.10	14.26	51.05	24.77	45.79	52.55	139.64	36.79	30.78	48.05	17.27	75.07	48.05	17.27	75.07
11	22.52	102.85	131.38	13.51	37.54	37.54	29.28	123.12	25.53	26.28	21.77	120.12	26.28	21.77	120.12
12	138.89	119.37	66.82	22.52	39.79	27.03	132.88	37.54	38.29	19.52	36.04	62.31	19.52	36.04	62.31
13	44.29	84.83	43.54	19.52	86.33	39.04	114.11	112.81	60.06	53.30	18.77	26.28	53.30	18.77	26.28
14	148.65	27.03	66.06	14.26	24.02	30.03	90.84	55.55	60.06	53.30	18.77	50.30	53.30	18.77	50.30
15	135.13	33.03	43.54	29.28	36.04	23.27	40.54	35.28	42.04	58.56	13.51	39.79	58.56	13.51	39.79
16	128.38	1.50	29.28	19.52	27.78	18.02	122.37	61.56	12.76	12.01	67.57	19.52	12.01	67.57	19.52
17	134.38	43.54	105.85	45.79	26.53	15.77	30.03	34.53	119.37	18.02	30.03	40.54	18.02	30.03	40.54
18	152.40	102.85	22.52	15.77	41.29	13.51	37.54	54.05	54.05	24.77	15.77	16.52	24.77	15.77	16.52
19	81.08	53.30	41.30	40.54	51.80	12.01	107.36	122.37	106.60	13.51	45.79	55.55	13.51	45.79	55.55
20	83.33	39.04	13.51	19.52	78.63	26.28	118.62	19.52	18.02	75.82	31.53	30.03	75.82	31.53	30.03
21	34.53	46.55	73.57	13.51	138.89	84.83	131.38	51.05	71.32	25.53	15.77	17.27	25.53	15.77	17.27
22	55.55	76.58	78.08	152.40	27.78	24.02	42.04	30.03	96.85	28.53	20.27	27.03	28.53	20.27	27.03
23	67.57	114.86	63.81	21.77	44.29	66.82	74.32	41.29	30.03	12.01	20.27	28.53	12.01	20.27	28.53
24	26.28	85.58	98.35	26.28	30.78	39.79	38.29	38.29	23.27	21.02	18.77	26.28	18.77	26.28	26.28
25	63.06	86.33	51.05	23.27	36.79	16.52	30.03	117.12	104.35	27.78	26.28	12.76	27.78	26.28	12.76
26	26.28	123.87	50.30	31.53	134.38	182.43	65.31	72.07	24.02	39.04	32.28	58.56	32.28	58.56	32.28
27	36.79	174.17	30.78	22.52	28.53	27.78	120.12	108.86	29.28	34.53	12.76	24.77	34.53	12.76	24.77
28	24.77	39.04	120.12	20.27	32.28	20.27	141.14	25.53	25.53	21.77	15.01	46.55	21.77	15.01	46.55
29	129.68	44.29	156.90	35.28	36.79	117.12	144.89	64.56	57.06	38.29	16.52	42.04	38.29	16.52	42.04
30	168.92	55.55	112.61	16.52	47.30	170.42	27.78	137.38	28.53	15.77	34.53	33.78	15.77	34.53	33.78
31	86.33	93.84	68.32	33.78	45.79	43.54	74.32	74.32	93.84	23.27	24.02	30.03	23.27	24.02	30.03
32	196.69	111.86	95.34	17.27	32.28	30.03	45.04	70.57	77.33	48.80	19.52	37.54	48.80	19.52	37.54
33	86.33	71.32	60.06	28.53	15.77	108.11	49.55	126.87	48.80	14.26	15.77	41.29	14.26	15.77	41.29
34	29.28	33.03	145.84	30.78	52.55	120.12	21.02	34.53	96.09	24.77	18.77	141.89	24.77	18.77	141.89
35	48.05	75.07	111.86	52.55	35.28	56.31	38.29	74.32	96.85	42.04	30.78	35.28	42.04	30.78	35.28
36	174.17	138.89	26.28	28.53	28.53	18.02	135.88	56.31	133.63	30.03	20.27	29.28	30.03	20.27	29.28
37	87.84	150.90	26.28	36.79	50.30	27.03	84.08	51.80	95.34	15.01	16.52	42.79	15.01	16.52	42.79
38	111.86	173.42	65.31	54.05	48.05	34.53	102.85	99.10	44.29	45.04	25.53	36.79	45.04	25.53	36.79
39	85.58	181.68	219.22	31.53	38.29	54.80	26.28	59.31	103.60	18.77	26.28	27.78	18.77	26.28	27.78
40	112.61	108.86	196.69	44.29	16.52	20.27	167.41	45.04	116.36	37.54	30.78	27.78	37.54	30.78	27.78
41	24.77	111.11	180.93	52.55	57.06	85.58	93.84	92.34	29.28	30.03	29.28	94.59	30.03	29.28	94.59
42	109.61	100.60	186.18	24.77	57.06	21.77	99.85	27.78	12.76	21.77	27.78	18.77	21.77	27.78	18.77
43	33.03	63.06	195.94	24.77	63.06	19.52	65.31	130.63	34.53	48.05	27.03	25.53	48.05	27.03	25.53
44	69.82	76.58	33.78	39.04	52.55	24.77	36.79	43.54	99.85	26.28	33.03	22.52	26.28	33.03	22.52
45	24.02	39.79	75.82	39.04	71.32	27.78	154.65	28.53	31.53	25.53	22.52	27.78	25.53	22.52	27.78
46	72.82	34.53	207.95	86.33	114.11	16.52	32.28	148.65	132.88	21.77	27.03	12.76	21.77	27.03	12.76
47	117.12	146.39	70.57	28.53	50.30	44.29	107.36	42.04	123.67	61.56	21.02	18.02	61.56	21.02	18.02
48	87.09	62.31	54.05	84.83	48.05	19.52	31.53	37.54	77.33	65.31	27.03	40.54	65.31	27.03	40.54
49	130.63	73.57	161.41	138.14	64.56	28.53	169.87	87.09	26.28	24.77	23.27	33.03	24.77	23.27	33.03
50	73.57	124.62	115.61	159.91	27.03	92.34	120.87	102.10	35.28	24.77	68.32	102.85	24.77	68.32	102.85
Mean/Slide	83.24	79.17	89.29	40.67	49.20	47.16	82.75	58.18	59.52	29.95	27.70	41.08	29.95	27.70	41.08
Mean/animal															
Mean/dose															

FSR-IPL 070402 / CATECHOL / RHODIA

Test item:		Catéchol			Organ			STOMACH			1 <sup>st</sup> treatment			25/09/2007			26/09/2007		
Dose:		200 mg/kg/day (x2)																	
Animal N°	Slide No. BC-07-Code BC-07-13	6524			6521			6522			6525								
		224 A	224 B	224 C	225 A	225 B	225 C	226 A	226 B	226 C	227 A	227 B	227 C						
File No. BC-07-13	No. of cell	J1.xls	J2.xls	J3.xls	C1.xls	C2.xls	C3.xls	L1.xls	L2.xls	L3.xls	R1.xls	R2.xls	R3.xls						
		Tail length			Tail length			Tail length			Tail length								
1	1	12.76	84.83	23.27	37.54	24.77	17.27	53.30	51.05	25.53	15.01	43.54	39.04						
2	2	27.78	16.52	25.53	27.03	12.76	22.52	51.80	15.77	32.28	19.52	11.26	72.07						
3	3	42.04	50.30	30.78	21.02	33.78	39.79	53.30	40.54	39.79	73.57	30.78	70.57						
4	4	53.30	16.52	25.53	23.27	33.78	36.79	53.30	26.28	39.79	35.28	22.52	27.03						
5	5	35.28	18.77	24.77	22.52	21.77	52.55	19.52	106.60	43.54	17.27	71.32	95.34						
6	6	16.52	31.53	17.27	57.81	29.28	42.79	30.78	28.53	81.83	21.02	19.52	41.29						
7	7	18.77	28.53	42.79	62.31	13.51	36.04	21.77	27.03	28.53	36.79	29.28	47.30						
8	8	50.30	14.26	35.28	26.28	13.51	21.02	21.77	12.76	76.58	25.53	27.78	68.32						
9	9	33.03	29.28	26.28	14.26	49.55	17.27	27.78	45.79	27.78	43.54	21.77	26.28						
10	10	24.77	42.04	69.82	30.78	34.53	28.53	26.28	29.28	36.79	26.28	54.05	20.27						
11	11	26.28	50.30	25.53	18.02	12.76	22.52	72.82	24.77	36.79	102.85	27.03	17.27						
12	12	24.77	43.54	36.29	27.03	16.52	22.52	26.28	24.77	36.79	30.03	51.80	43.54						
13	13	18.77	26.28	21.77	14.26	17.27	27.78	16.52	75.07	108.86	51.80	14.26	90.09						
14	14	21.77	34.53	26.28	10.51	30.03	30.78	38.29	69.07	87.84	14.26	50.30	42.04						
15	15	27.78	66.82	36.79	73.57	11.26	17.27	67.57	54.80	27.78	15.77	33.03	75.07						
16	16	39.79	37.54	17.27	28.53	34.53	20.27	29.28	36.04	33.03	19.52	21.02	26.28						
17	17	57.81	26.28	91.59	41.29	18.02	22.52	24.77	18.02	20.27	25.53	27.03	29.28						
18	18	21.02	25.53	70.57	33.78	15.77	34.53	48.80	45.79	21.02	26.28	25.53	43.54						
19	19	19.52	29.28	16.52	24.77	27.03	60.06	23.27	25.53	24.77	48.80	27.78	21.77						
20	20	13.51	11.11	52.55	36.79	24.77	23.27	13.51	18.77	53.30	18.02	32.28	20.27						
21	21	15.01	99.10	27.78	27.78	23.27	20.27	11.26	39.79	108.86	49.55	94.59	35.28						
22	22	16.52	27.03	33.78	20.27	16.52	21.02	75.07	34.53	13.51	17.27	19.52	79.58						
23	23	35.28	34.53	36.29	30.03	45.04	11.26	71.32	16.52	51.80	36.79	27.03	66.06						
24	24	22.52	27.03	18.02	56.31	39.04	39.04	25.53	47.30	24.02	63.06	36.04	24.77						
25	25	30.78	27.78	34.53	33.03	21.77	33.78	53.30	67.57	88.59	44.29	78.83	45.04						
26	26	13.51	43.54	26.28	29.28	26.28	26.28	41.29	28.53	15.01	22.52	30.78	30.03						
27	27	27.78	18.02	12.01	12.01	12.76	31.53	18.77	76.58	25.53	12.76	41.29	13.51						
28	28	15.77	28.53	34.53	16.52	20.27	52.55	39.04	26.28	66.82	20.27	12.01	53.30						
29	29	20.27	39.04	75.82	11.26	15.77	48.80	18.77	45.79	10.51	35.28	39.79	91.59						
30	30	26.28	27.03	47.30	13.51	18.77	43.54	42.04	37.54	81.08	48.80	26.28	21.02						
31	31	27.03	25.53	63.06	24.77	24.77	19.52	51.80	43.54	21.77	27.03	24.02	33.03						
32	32	16.52	12.76	21.77	14.26	13.51	11.26	48.80	36.79	27.78	60.06	14.26	59.31						
33	33	26.28	21.77	19.52	13.51	25.53	45.04	26.28	13.51	76.58	39.04	81.08	21.77						
34	34	39.79	25.53	99.85	21.77	21.77	53.30	61.56	101.35	60.81	24.02	45.04	33.03						
35	35	17.27	33.03	39.04	34.53	14.26	58.56	68.32	50.30	30.78	60.81	21.02	59.31						
36	36	28.53	23.27	35.28	30.78	21.77	37.54	12.76	16.52	29.28	21.77	91.59	18.77						
37	37	46.55	24.77	33.78	36.04	14.26	26.28	89.34	16.52	61.56	63.06	24.77	15.01						
38	38	23.27	26.28	52.55	41.29	14.26	16.52	86.33	28.53	125.37	20.27	57.06	33.78						
39	39	19.52	78.83	16.52	57.81	34.53	54.05	29.28	51.05	75.82	76.56	32.28	33.78						
40	40	60.06	27.03	27.78	27.78	33.03	10.51	50.30	99.10	46.55	54.80	18.02	15.77						
41	41	26.28	40.54	45.79	15.01	73.57	27.78	36.79	28.53	35.28	21.02	42.04	42.79						
42	42	60.06	21.77	36.04	32.28	21.77	14.26	39.04	82.58	72.07	68.32	30.78	50.30						
43	43	27.03	17.27	44.29	21.02	25.53	50.30	20.27	30.03	36.79	33.78	14.26	25.53						
44	44	30.78	15.01	26.28	30.03	54.05	27.78	42.79	19.52	28.53	30.78	36.04	57.81						
45	45	25.53	21.02	33.78	26.28	22.52	12.76	42.04	28.53	33.78	39.79	27.03	23.27						
46	46	20.27	22.52	19.52	18.02	25.53	68.32	17.27	41.29	24.77	27.78	69.82	26.28						
47	47	64.56	15.77	42.79	15.01	27.78	48.05	84.08	36.04	28.53	30.78	65.31	14.26						
48	48	50.30	15.01	138.14	25.53	31.53	66.82	14.26	21.02	37.54	27.03	42.79	45.04						
49	49	75.82	26.28	18.02	30.03	60.06	75.82	57.81	53.30	65.31	27.03	21.77	36.79						
50	50	18.77	37.54	34.53	16.52	54.05	28.53	12.76	27.78	79.58	60.06	25.53	25.53						
Mean/slide		30.27	33.74	38.30	28.27	26.41	33.32	39.71	40.45	47.45	36.71	36.65	40.96						
Mean/animal		36.02																	
Mean/dose		36.11																	

## FSR-IPL 070402 / CATECHOL / RHODIA

Test item:		Catechol		Organ		STOMACH		1 <sup>st</sup> treatment:		25/09/2007		26/09/2007	
Dose:		100 mg/kg/day (x2)		6527		6529		6526		6530			
Animal N°		228 A	228 B	228 C	229 A	229 B	229 C	230 A	230 B	230 C	231 A	231 B	231 C
Slide No. BC-07-13		I1.xls	I2.xls	I3.xls	P1.xls	P2.xls	P3.xls	M1.xls	M2.xls	M3.xls	H1.xls	H2.xls	H3.xls
File No. BC-07-13		I1.xls	I2.xls	I3.xls	P1.xls	P2.xls	P3.xls	M1.xls	M2.xls	M3.xls	H1.xls	H2.xls	H3.xls
No. of cell		I1.xls	I2.xls	I3.xls	P1.xls	P2.xls	P3.xls	M1.xls	M2.xls	M3.xls	H1.xls	H2.xls	H3.xls
1		27.03	26.28	74.32	27.03	15.01	143.39	33.78	39.04	34.53	35.28	28.53	12.76
2		9.76	27.03	76.58	49.55	78.08	36.04	57.81	28.53	37.54	26.28	69.82	36.04
3		36.04	40.54	36.04	48.80	33.03	36.79	56.31	26.28	22.52	60.06	71.32	42.79
4		23.27	66.06	32.28	60.81	27.78	49.55	36.04	24.02	30.03	37.54	31.53	45.04
5		50.30	31.53	47.30	18.77	83.33	17.77	25.53	18.02	65.31	32.28	75.07	66.82
6		108.86	18.02	15.01	28.53	14.26	17.27	22.52	17.27	101.35	40.54	111.11	71.32
7		29.28	51.05	6.76	42.04	97.60	37.54	33.03	17.27	44.29	27.78	45.04	54.80
8		32.28	18.02	36.04	33.03	24.77	113.36	21.02	44.29	26.28	33.78	45.04	30.78
9		25.53	21.77	22.52	33.78	88.59	62.31	93.84	27.78	63.06	39.04	31.53	46.55
10		27.78	9.76	57.81	33.03	66.82	33.03	90.84	26.28	87.84	26.28	69.07	50.30
11		26.28	12.76	30.03	24.77	107.36	26.28	22.52	26.28	84.08	21.02	29.28	63.06
12		51.05	46.55	27.78	45.79	42.04	12.01	39.04	26.28	68.32	73.57	15.01	125.37
13		18.77	33.03	82.58	32.28	42.04	29.28	48.80	47.30	11.26	39.79	40.54	57.81
14		30.78	46.55	26.28	61.56	32.28	69.07	82.58	57.81	33.03	20.27	36.79	26.28
15		21.02	27.03	69.82	27.03	78.08	27.03	49.55	22.52	46.55	70.57	25.53	126.87
16		33.03	27.03	37.54	40.54	80.33	20.27	10.51	101.35	21.77	55.55	41.29	25.53
17		49.55	33.78	51.80	25.53	54.05	26.28	62.31	24.77	27.78	44.29	84.83	64.56
18		16.52	31.53	45.79	14.26	56.31	42.04	30.78	31.53	203.45	18.77	21.77	21.02
19		66.06	65.31	63.81	18.02	30.78	30.03	21.77	27.78	96.09	36.04	36.04	90.84
20		30.78	95.34	25.53	35.28	81.08	22.52	60.06	14.26	13.51	36.04	28.53	24.02
21		100.60	89.34	46.05	27.03	30.03	55.55	59.31	25.53	24.77	42.79	36.79	69.82
22		34.53	30.78	101.35	12.01	54.05	126.12	33.03	54.05	90.09	36.04	45.79	42.79
23		42.79	40.54	111.86	92.34	54.80	31.53	18.02	27.03	36.79	43.54	36.79	52.55
24		30.03	27.03	33.03	26.28	34.53	74.32	31.53	21.02	84.83	13.51	69.07	34.53
25		15.01	33.03	87.84	34.53	28.53	28.53	48.80	33.78	75.82	27.03	29.28	37.54
26		12.01	54.05	39.04	50.30	49.55	27.03	48.05	30.03	117.12	18.02	46.55	66.82
27		39.79	43.54	27.78	50.30	29.28	37.54	40.54	27.03	38.29	37.54	33.03	25.53
28		30.78	55.55	27.03	90.84	38.29	80.33	33.03	13.51	75.82	69.82	33.03	69.82
29		47.30	35.28	45.79	48.80	42.04	79.58	21.77	112.61	66.82	15.01	37.54	82.58
30		72.82	24.77	26.28	23.27	30.78	30.78	89.34	12.76	18.77	35.28	14.26	52.55
31		24.02	18.02	30.03	21.02	30.03	58.56	55.55	35.28	70.57	13.51	27.78	18.77
32		39.79	57.81	39.79	36.79	50.30	29.28	33.03	110.36	44.29	15.77	66.06	52.55
33		22.52	54.80	14.26	38.29	30.78	32.28	44.29	27.03	26.28	57.81	66.06	24.77
34		117.87	31.53	54.80	53.03	33.78	41.29	32.28	15.77	45.79	147.14	53.30	43.54
35		29.28	45.79	72.82	51.80	57.06	95.34	29.28	15.01	75.82	47.30	36.29	38.29
36		24.02	27.03	87.09	44.29	103.60	50.30	35.28	19.52	46.55	35.28	24.02	99.10
37		24.02	54.80	14.26	48.80	156.15	94.59	79.58	36.79	43.54	25.53	23.27	19.52
38		60.06	27.03	43.54	51.05	81.08	75.07	39.79	27.03	17.27	90.84	36.79	123.12
39		138.89	111.86	45.79	19.52	37.54	58.56	15.01	83.33	31.53	71.32	34.53	74.32
40		60.81	31.53	18.77	54.80	147.14	195.19	27.03	52.55	53.30	31.53	42.79	39.04
41		77.33	25.53	73.57	26.28	60.06	26.28	48.80	85.58	30.78	47.30	36.04	108.86
42		50.30	42.79	30.78	106.60	78.08	73.57	27.78	78.83	47.30	54.05	41.29	39.04
43		16.52	34.53	93.09	28.53	77.33	59.31	17.27	78.83	86.33	114.86	25.53	49.55
44		22.52	60.81	84.83	39.79	23.27	28.53	55.55	18.77	93.09	14.26	67.57	29.28
45		33.03	51.80	33.03	28.53	31.53	20.27	19.52	51.05	123.12	46.55	22.52	84.08
46		117.12	60.81	63.81	48.80	26.28	120.12	18.02	30.03	20.27	41.29	57.06	37.54
47		46.55	64.56	50.30	21.02	42.04	47.30	94.59	66.82	26.28	28.53	29.28	60.06
48		26.28	28.53	33.78	21.02	24.77	57.81	43.54	126.87	56.31	48.05	48.55	59.31
49		29.28	63.81	30.03	33.03	36.79	36.79	69.07	45.79	93.09	38.29	26.28	50.30
50		31.53	40.54	57.06	29.28	75.07	78.83	67.57	27.03	51.05	104.35	55.55	39.79
Mean/Slide		42.63	41.94	47.70	38.86	54.41	54.31	43.50	40.57	56.29	43.74	42.49	54.16
Mean/Animal		42.63	41.94	47.70	38.86	54.41	54.31	43.50	40.57	56.29	43.74	42.49	54.16
Mean/dose		44.09	44.09	47.70	38.86	49.19	46.72	46.72	46.79	46.79	46.79	46.80	46.80

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## Appendix No. 9: Individual values for Percentage of DNA / STOMACH

Test item: Dose:	Animal N°	Distilled water 0 mg/kg/day (x2)		Organ:	STOMACH		1 <sup>st</sup> treatment: 2 <sup>nd</sup> treatment		25/09/2007 26/09/2007		6515			
		Slide No. BC-07- Code BC-07-13 File No. BC-07-13	No. of cell		213 A	213 B	213 C	214 A	214 B	214 C	215 A	215 B	215 C	216 A
		Q1.xls	Q2.xls	Q3.xls	Q1.xls	Q2.xls	Q3.xls	E1.xls	E2.xls	E3.xls	G1.xls	G2.xls	G3.xls	
		% DNA in tail			% DNA in tail			% DNA in tail			% DNA in tail			
1	1	18.17	7.33	9.62	0.36	5.45	0.05	20.34	60.97	23.10	7.98	4.55	17.17	
2	2	21.38	3.72	43.68	15.55	15.33	33.21	16.49	7.64	3.13	59.50	66.34	1.03	
3	3	24.12	11.81	2.08	26.16	10.19	2.90	15.05	6.91	0.97	9.57	2.05	0.33	
4	4	22.19	0.11	10.27	3.15	0.68	14.78	38.78	44.71	13.46	4.67	66.59	62.62	
5	5	2.61	28.29	19.79	1.68	19.80	9.37	3.85	87.46	6.51	6.32	5.58	4.62	
6	6	20.44	14.28	69.58	7.54	29.13	0.42	89.15	98.58	22.17	8.66	5.87	17.61	
7	7	13.85	7.12	1.34	29.28	19.18	2.84	83.80	83.04	13.63	4.72	6.23	3.37	
8	8	4.05	2.08	42.35	10.21	15.52	4.76	45.13	69.62	4.88	2.32	70.03	32.61	
9	9	15.48	6.18	5.70	12.88	1.34	27.12	7.91	42.58	23.48	29.37	1.79	1.19	
10	10	20.37	3.00	26.17	17.84	11.04	1.42	21.88	57.89	1.61	49.67	0.48	29.65	
11	11	1.37	12.49	24.42	11.17	57.52	6.87	5.59	15.35	38.00	9.78	0.11	0.11	
12	12	10.25	1.50	24.97	42.67	91.16	11.09	5.34	0.45	1.87	19.45	66.38	41.85	
13	13	5.48	51.51	45.66	21.45	9.44	24.80	73.46	61.71	4.87	60.74	0.88	0.79	
14	14	14.61	17.60	7.39	18.05	1.40	6.14	14.94	51.40	2.67	74.87	1.82	40.16	
15	15	22.09	31.25	0.94	1.05	3.97	1.57	2.58	6.25	18.47	49.54	7.79	7.79	
16	16	15.39	21.72	1.30	6.39	3.44	23.58	50.17	67.94	3.16	0.34	52.89	48.03	
17	17	6.39	2.40	57.22	8.72	17.87	6.00	52.50	7.38	0.81	58.50	26.27	50.72	
18	18	26.38	0.34	8.63	21.96	11.53	3.73	62.67	24.70	51.26	2.03	7.77	0.30	
19	19	12.70	2.37	4.02	25.93	6.86	7.97	0.20	89.49	7.26	31.06	3.26	28.42	
20	20	6.69	1.18	6.88	1.16	0.84	0.18	24.85	88.63	7.48	44.96	17.63	11.75	
21	21	18.85	22.05	0.00	16.72	7.14	1.91	28.04	35.76	17.09	8.26	16.75	5.15	
22	22	6.39	1.41	12.44	3.71	0.80	0.03	89.06	50.43	50.91	13.67	10.19	71.43	
23	23	43.26	0.00	14.97	4.99	2.30	29.86	51.57	92.78	16.17	84.17	49.91	10.88	
24	24	5.90	16.83	24.91	13.03	18.79	1.71	14.30	9.15	58.01	52.01	51.32	19.67	
25	25	26.22	17.56	30.95	18.88	5.51	11.06	82.59	34.76	29.24	28.65	9.24	11.86	
26	26	93.46	11.67	20.04	27.52	14.99	11.97	31.66	42.35	7.82	0.97	28.20	25.49	
27	27	14.53	18.56	39.00	13.85	0.84	11.29	52.62	37.28	5.43	3.49	14.78	14.41	
28	28	9.96	3.62	15.46	19.65	12.12	8.22	38.18	7.07	5.48	33.72	0.03	48.97	
29	29	31.02	19.34	24.55	2.04	0.72	8.83	3.27	16.26	4.28	5.05	2.53	0.30	
30	30	1.21	8.65	4.76	43.28	3.04	2.81	33.58	88.84	33.03	72.91	29.66	2.07	
31	31	0.64	31.43	11.76	0.57	1.00	3.20	46.54	45.43	1.33	2.39	9.92	56.01	
32	32	15.98	0.32	2.89	6.16	9.40	0.25	26.42	21.51	43.50	51.74	4.80	1.05	
33	33	50.65	30.89	73.81	2.31	41.42	0.38	65.03	9.35	0.04	0.81	28.02	1.12	
34	34	11.65	1.51	9.46	31.93	5.26	0.56	28.64	31.59	25.99	4.04	17.85	6.26	
35	35	0.50	15.11	10.98	14.35	7.18	14.99	8.96	10.19	5.91	49.79	48.39	7.68	
36	36	0.20	0.15	21.65	18.78	43.94	23.30	33.96	76.36	22.59	20.99	33.88	18.74	
37	37	4.40	19.43	14.03	0.33	6.14	0.55	65.36	4.85	26.28	15.35	45.23	40.53	
38	38	13.05	3.15	22.81	13.72	13.15	38.21	77.74	66.74	47.91	73.73	0.24	26.43	
39	39	1.53	1.82	4.28	8.32	0.80	49.13	25.30	20.46	4.74	43.12	59.66	22.28	
40	40	40.03	4.53	17.50	26.06	1.60	0.92	81.48	35.28	0.99	0.79	0.64	56.73	
41	41	62.62	41.42	42.70	7.24	1.89	2.05	49.80	78.99	24.72	51.02	2.64	49.84	
42	42	10.47	0.36	35.01	9.78	0.90	12.75	55.41	91.15	6.22	8.12	4.06	53.74	
43	43	0.02	2.81	26.22	44.65	4.67	7.31	48.09	13.73	0.92	22.10	3.52	9.02	
44	44	2.59	26.44	19.84	26.43	0.06	0.60	85.29	76.37	1.45	52.85	9.02	5.34	
45	45	3.95	0.40	23.15	13.22	0.04	11.82	76.91	40.68	13.94	0.57	0.39	39.91	
46	46	7.73	10.64	9.15	21.27	2.69	9.38	34.70	0.98	34.37	48.88	42.64	19.87	
47	47	29.91	0.00	13.49	9.67	6.96	2.32	18.49	69.23	2.62	71.46	0.46	30.53	
48	48	11.73	20.75	4.40	1.80	11.16	18.05	72.59	93.33	29.51	44.65	6.85	23.44	
49	49	1.00	2.29	31.82	0.10	26.43	5.01	15.92	25.21	40.35	1.77	4.12	0.48	
50	50	6.49	5.39	17.17	1.51	20.19	5.01	90.79	56.55	47.32	13.11	6.92	43.60	
Mean/slide		16.20	11.45	20.22	14.09	12.04	9.65	41.18	43.63	17.36	21.62	20.14	22.72	
Mean/dose			15.96			11.93			34.05			23.49		
								21.36						

Test item:		Catechol		Organ:		STOMACH		1 <sup>st</sup> treatment:		25/09/2007		26/09/2007	
Dose:		400 mg/kg/day (x2)											
Animal N°	Slide No. BC-07-13	6518		6517		6520		6519					
		220 A	220 B	220 C	221 A	221 B	221 C	222 A	222 B	222 C	223 A	223 B	223 C
File No. BC-07-13	No. of cell	B1.xls	B2.xls	B3.xls	K1.xls	K2.xls	K3.xls	D1.xls	D2.xls	D3.xls	S1	S2	S3
		% DNA in tail	% DNA in tail	% DNA in tail	% DNA in tail	% DNA in tail	% DNA in tail	% DNA in tail	% DNA in tail	% DNA in tail	% DNA in tail	% DNA in tail	% DNA in tail
1	1	4.25	0.38	4.53	2.37	45.00	1.34	38.89	50.86	0.10	0.45	31.18	1.43
2	2	6.89	0.27	9.75	4.31	1.85	1.98	7.22	5.36	65.58	0.05	2.28	14.30
3	3	73.52	3.64	28.05	0.05	2.16	1.94	4.37	6.40	1.27	0.14	19.92	6.96
4	4	1.73	0.22	12.21	36.05	10.48	1.10	4.04	36.40	2.76	1.17	0.43	1.15
5	5	1.92	65.11	1.07	1.30	1.02	0.09	96.67	12.91	4.11	0.15	6.27	4.19
6	6	0.09	44.40	1.68	1.04	0.20	4.25	8.31	4.34	30.93	3.32	34.75	2.71
7	7	25.41	0.81	81.20	22.48	0.08	30.48	10.17	84.99	25.87	0.04	0.17	0.78
8	8	0.25	94.45	47.14	0.00	11.72	0.08	95.92	10.46	15.42	0.06	0.66	0.97
9	9	74.82	2.60	25.37	1.41	1.45	16.12	1.57	59.13	1.28	0.07	8.50	0.41
10	10	19.30	0.34	5.56	1.22	4.11	0.96	69.24	0.94	1.00	12.36	1.13	26.07
11	11	27.79	66.94	6.54	0.78	11.52	2.67	3.18	91.65	0.56	0.02	0.04	43.68
12	12	65.04	85.39	6.54	0.36	2.32	0.15	79.96	11.54	19.15	0.11	13.13	3.22
13	13	5.34	56.83	3.55	0.68	77.65	9.33	19.05	68.92	0.06	0.00	5.88	0.28
14	14	79.30	1.01	5.73	0.00	0.53	1.22	16.18	28.65	8.85	11.39	0.14	3.07
15	15	90.97	9.36	3.01	1.36	0.50	0.70	7.13	0.63	0.79	5.11	0.82	1.80
16	16	64.95	19.15	2.71	0.90	0.32	0.03	83.41	5.47	0.00	0.01	25.42	0.10
17	17	51.47	1.38	71.42	2.97	3.91	0.27	12.30	69.75	0.27	1.53	2.38	2.38
18	18	83.13	15.18	0.25	0.34	3.77	1.49	22.71	11.47	19.13	0.70	0.00	4.75
19	19	14.01	23.80	2.15	4.32	9.02	0.00	39.29	58.34	48.81	0.00	17.21	12.16
20	20	30.54	0.13	1.09	8.70	55.76	2.65	28.46	4.35	0.13	35.80	1.27	0.06
21	21	15.35	2.85	24.79	0.78	16.37	5.90	39.88	24.20	18.74	2.74	0.00	1.20
22	22	29.98	39.27	47.61	62.15	0.18	0.13	3.92	0.02	56.67	7.50	0.00	0.02
23	23	14.30	32.59	8.56	0.25	12.82	14.50	11.60	16.82	0.82	7.89	0.22	1.07
24	24	0.35	48.25	18.07	0.25	3.90	0.51	6.63	4.35	0.01	8.41	2.12	0.12
25	25	33.40	33.22	6.50	1.55	0.78	8.17	8.55	65.42	43.36	23.25	2.54	0.31
26	26	5.18	44.45	6.95	0.67	94.70	81.84	16.37	8.77	0.34	4.59	3.18	1.50
27	27	30.90	40.35	0.10	1.54	0.68	1.21	57.68	48.60	1.21	3.37	0.29	0.01
28	28	1.36	11.90	74.38	1.33	0.74	0.97	52.70	0.40	0.04	0.41	2.94	3.66
29	29	24.06	6.04	67.99	6.17	0.68	67.39	87.18	11.36	1.98	3.30	0.41	2.07
30	30	47.26	4.46	83.40	0.94	11.87	37.74	4.63	32.41	2.26	0.23	11.84	12.17
31	31	24.59	38.81	25.53	5.76	2.33	15.52	41.82	34.17	34.32	0.79	0.07	3.57
32	32	41.11	19.29	25.31	3.41	9.89	7.66	6.77	28.57	16.17	12.24	6.34	0.21
33	33	39.14	1.69	7.18	9.45	1.23	20.47	8.55	62.03	11.00	0.69	0.18	1.36
34	34	3.99	0.92	83.84	3.35	16.99	89.33	1.06	2.55	30.56	0.03	4.87	58.49
35	35	1.86	12.50	30.03	11.16	0.40	10.52	8.97	18.41	9.28	2.83	0.02	0.30
36	36	34.81	75.97	1.48	7.98	1.45	0.15	31.61	24.44	62.01	0.30	8.41	0.04
37	37	45.30	72.89	1.66	40.59	9.83	3.08	41.35	27.88	38.47	0.18	0.14	9.59
38	38	58.77	88.74	56.49	81.55	13.75	1.95	37.67	70.82	3.15	0.50	7.04	0.23
39	39	18.71	57.65	27.73	10.12	9.90	13.33	7.31	17.56	38.11	0.78	8.94	0.08
40	40	60.26	6.13	88.19	18.35	10.78	0.49	55.83	9.93	30.42	7.78	7.43	0.27
41	41	1.61	41.53	84.28	15.37	15.96	12.74	9.43	34.12	4.05	0.47	0.71	16.36
42	42	19.20	93.82	71.38	0.74	22.47	4.40	44.93	0.66	0.06	3.92	1.14	0.77
43	43	1.71	37.53	95.47	4.54	27.64	0.02	30.50	58.11	0.11	20.52	0.82	0.95
44	44	25.41	30.03	3.89	4.52	4.42	0.12	1.57	10.08	13.48	0.28	3.80	3.16
45	45	3.67	0.23	12.62	4.56	17.47	3.02	72.71	0.09	1.92	0.03	0.53	1.43
46	46	36.84	1.22	93.71	39.36	50.09	0.09	1.09	31.59	49.08	0.03	1.47	0.00
47	47	85.65	47.52	15.75	2.16	6.87	6.32	69.90	11.85	61.12	1.11	1.47	0.07
48	48	11.76	18.72	11.96	40.09	19.59	0.01	15.09	1.36	23.02	35.38	0.81	0.86
49	49	85.98	57.39	46.77	82.80	17.78	32.07	81.44	45.70	0.85	1.32	1.32	0.29
50	50	26.26	57.21	72.12	84.63	0.75	8.77	86.68	56.89	1.98	1.33	20.22	37.88
Mean/slide		30.48	29.51	31.47	12.73	12.81	10.51	31.99	26.48	17.40	4.62	5.39	5.77
Mean/animal		18.27											
Mean/dose		30.49											

Test item Dose:	Catéchol 200 mg/kg/day (x2)	Organ	STOMACH	1 <sup>st</sup> treatment		2 <sup>nd</sup> treatment		25/09/2007		26/09/2007									
				6524			6521			6522			6525						
				224 A		224 B	224 C	225 A		225 B	225 C	226 A		226 B	226 C	227 A		227 B	227 C
				J1.xls	J2.xls	J3.xls	C1.xls	C2.xls	C3.xls	L1.xls	L2.xls	L3.xls	R1.xls	R2.xls	R3.xls				
File No. BC-07-13	J1.xls	J2.xls	J3.xls	C1.xls	C2.xls	C3.xls	L1.xls	L2.xls	L3.xls	R1.xls	R2.xls	R3.xls							
No. of cell	% DNA in tail			% DNA in tail			% DNA in tail			% DNA in tail									
1	0.00	34.29	1.78	0.02	9.97	0.30	54.76	26.78	1.49	0.02	6.05	15.21							
2	96.53	0.06	1.26	0.14	2.92	4.83	70.21	1.17	0.31	0.03	0.00	21.76							
3	12.11	3.50	0.22	3.03	0.23	0.22	8.43	17.28	1.33	18.93	6.06	70.78							
4	41.63	0.35	0.29	0.16	12.62	0.21	32.89	0.09	1.68	94.74	5.58	17.62							
5	1.67	0.51	4.21	1.82	1.29	15.37	2.49	91.47	4.00	0.01	18.10	60.90							
6	1.87	1.14	1.62	12.44	5.27	0.31	12.22	16.77	30.79	2.28	0.37	0.18							
7	0.00	1.27	14.16	31.19	0.20	17.59	2.65	0.16	7.51	5.09	0.14	20.75							
8	9.33	0.41	36.43	0.05	0.54	8.31	6.80	0.02	4.36	1.14	2.15	13.48							
9	26.52	3.53	0.36	1.43	56.05	0.03	10.14	14.15	16.41	4.47	0.43	4.73							
10	10.93	0.99	96.43	5.42	40.52	2.43	2.65	10.49	4.38	0.52	2.30	0.01							
11	11.47	12.79	0.92	1.42	0.08	0.02	9.42	1.88	1.42	95.24	0.90	0.01							
12	1.33	80.47	0.68	0.10	2.07	1.07	1.57	3.85	1.13	2.81	3.42	24.56							
13	0.01	2.89	0.16	0.02	0.37	0.26	2.65	1.76	27.99	19.71	4.37	41.61							
14	7.51	4.07	0.01	1.51	0.02	0.90	35.49	5.69	21.83	0.01	3.52	3.69							
15	16.11	18.01	1.15	80.88	0.00	0.04	23.10	94.42	1.64	0.53	8.81	22.98							
16	9.32	7.68	0.01	0.88	7.63	4.67	0.37	5.16	3.77	0.04	0.27	0.55							
17	24.47	1.12	26.79	4.33	0.02	0.19	0.35	3.65	0.88	0.10	1.01	0.62							
18	0.48	2.86	8.54	13.76	5.21	0.18	13.00	30.80	0.61	1.07	2.79	6.02							
19	1.34	0.07	0.03	0.05	3.19	45.88	0.51	0.14	2.68	11.90	0.69	0.01							
20	0.23	92.17	13.67	4.49	24.68	5.37	0.01	1.22	26.62	1.08	0.26	0.51							
21	0.07	29.21	0.74	5.07	0.00	3.37	0.05	25.43	50.91	17.32	66.00	11.63							
22	4.10	1.15	2.07	0.07	0.48	0.00	93.64	24.24	4.48	0.00	0.12	39.97							
23	0.66	3.54	1.60	0.10	49.89	0.02	22.99	4.13	85.50	6.83	1.22	97.48							
24	0.06	3.86	0.18	53.98	17.66	14.19	22.53	5.91	3.92	65.29	2.73	1.80							
25	11.38	0.78	2.60	0.49	1.07	18.19	10.95	23.56	47.00	12.72	47.91	29.99							
26	0.23	2.84	5.60	0.18	0.04	7.37	20.40	2.33	0.07	4.08	17.92	12.40							
27	1.53	0.88	1.32	0.21	0.45	10.12	2.24	43.76	11.13	0.03	0.99	0.00							
28	0.89	2.45	0.06	0.03	0.03	12.98	13.62	7.00	49.76	0.01	0.00	19.03							
29	3.09	10.58	6.50	0.00	0.75	26.24	4.18	26.76	0.31	3.67	5.50	71.65							
30	0.05	3.54	5.36	0.98	2.39	27.88	16.58	8.70	91.96	19.76	0.22	6.43							
31	1.79	0.40	34.33	0.00	3.72	14.52	10.79	1.66	1.92	0.01	11.54	22.66							
32	0.25	0.00	1.06	0.09	0.50	0.00	20.32	10.15	0.68	37.83	0.00	7.17							
33	0.02	0.21	3.96	0.01	0.02	9.06	1.44	0.00	29.85	20.77	49.34	1.72							
34	2.72	0.26	47.16	12.56	20.93	11.33	97.43	30.54	8.42	0.11	5.98	4.87							
35	0.02	10.16	16.11	0.18	1.85	12.16	88.75	36.69	2.76	21.47	8.60	37.57							
36	0.18	0.94	2.14	0.78	8.77	7.33	0.00	0.06	3.96	4.04	43.51	4.71							
37	0.90	2.70	0.49	1.73	3.49	0.63	21.38	0.61	4.22	15.39	0.29	1.13							
38	8.25	0.21	60.33	5.28	0.00	0.01	42.49	0.61	50.66	4.54	34.26	4.17							
39	0.13	19.52	0.02	23.90	13.79	0.09	0.95	6.62	12.01	25.69	2.64	1.46							
40	28.19	0.24	0.58	4.86	3.09	1.10	26.90	22.46	4.20	21.64	1.33	0.02							
41	0.64	1.29	2.82	0.06	78.06	4.10	4.57	1.10	1.02	1.82	3.08	2.88							
42	20.50	8.12	4.96	0.18	0.12	0.53	3.12	61.02	1.60	9.64	3.09	15.58							
43	0.68	0.09	3.25	0.28	0.51	26.98	5.77	1.33	1.97	8.23	2.10	0.00							
44	0.84	0.31	0.26	0.59	15.48	3.26	4.09	1.09	5.45	6.33	7.30	16.01							
45	0.01	0.12	3.67	1.89	2.12	0.00	7.56	0.03	0.93	6.00	0.04	0.03							
46	0.74	0.74	1.26	3.34	4.19	20.47	0.34	18.53	1.49	1.65	30.98	0.26							
47	52.51	0.28	2.75	7.40	0.14	4.83	91.27	0.03	3.63	9.50	28.55	0.00							
48	16.34	0.06	80.26	0.07	0.45	5.24	0.00	0.03	0.01	12.02	1.97	27.98							
49	40.01	0.00	0.03	8.15	25.48	14.43	25.48	98.61	30.39	8.62	0.01	3.37							
50	0.40	2.99	2.94	0.69	1.28	5.95	0.98	12.23	20.21	2.85	0.01	0.88							
Mean/slide	9.40	7.51	10.06	5.93	8.59	7.45	19.01	16.17	13.83	12.15	8.89	15.38							
Mean/dose	11.20																		

## FSR-IPL 070402 / CATECHOL / RHODIA

Test item	Catéchol 100 mg/kg/day (x2)	Organ:	STOMACH		1 <sup>st</sup> treatment:		25/09/2007		26/09/2007			
			Dose:		2 <sup>nd</sup> treatment:		6526		6530			
Animal N°	228 A	228 B	228 C	229 A	229 B	229 C	230 A	230 B	230 C	231 A	231 B	231 C
Slide No. BC-07-13	I1	I2	I3	P1	P2	P3	M1	M2	M3	H1	H2	H3
File No. BC-07-13	11.xls	12.xls	13.xls	P1.xls	P2.xls	P3.xls	M1.xls	M2.xls	M3.xls	H1.xls	H2.xls	H3.xls
No. of cell	% DNA in tail			% DNA in tail			% DNA in tail			% DNA in tail		
1	6.61	0.10	19.75	0.47	0.24	39.88	1.76	13.32	2.83	10.78	10.30	1.13
2	0.39	2.44	13.08	13.24	41.58	11.55	30.23	2.75	6.41	4.94	45.50	2.86
3	15.33	17.04	0.10	8.97	31.53	2.11	31.86	2.11	3.07	3.26	14.36	1.67
4	14.71	18.06	2.42	9.09	3.13	16.75	14.62	4.21	3.07	4.30	4.83	4.06
5	8.80	4.34	19.95	0.01	15.54	4.21	5.47	0.01	7.10	5.88	11.68	4.63
6	48.36	15.56	1.04	2.59	7.98	1.80	1.50	1.30	13.14	17.11	42.85	41.24
7	1.55	25.54	0.00	2.81	56.16	13.67	1.68	2.42	4.09	6.12	11.60	8.24
8	5.41	0.38	7.52	4.13	10.40	36.46	2.17	7.42	0.35	19.99	9.50	2.07
9	0.49	2.08	2.93	3.98	33.65	3.08	2.47	13.54	96.28	3.73	1.98	4.97
10	9.05	1.23	24.37	3.12	26.43	1.78	41.22	3.29	13.35	0.82	45.16	5.34
11	8.25	2.56	4.85	1.50	22.64	19.90	8.57	10.42	96.25	1.22	1.77	28.88
12	7.96	14.23	2.28	26.24	11.83	1.83	23.09	15.27	12.52	46.66	2.21	18.19
13	1.63	94.40	32.85	11.00	1.26	5.20	7.50	4.49	0.71	12.39	2.43	92.30
14	8.12	22.69	2.98	10.10	7.42	28.20	45.02	35.34	6.66	0.23	1.30	0.61
15	12.57	0.00	60.84	0.79	56.31	1.52	4.49	2.59	97.16	36.69	0.41	93.48
16	42.94	22.89	13.44	8.25	33.08	0.05	0.79	42.84	0.01	21.62	3.46	3.23
17	13.51	3.75	6.48	1.02	5.56	2.01	35.91	2.47	0.01	24.73	34.60	11.25
18	6.39	6.94	1.96	0.44	13.52	24.91	36.48	4.04	39.59	7.87	0.63	0.93
19	18.69	20.22	15.60	4.60	2.97	0.86	1.16	12.20	94.54	6.19	0.29	68.92
20	0.51	49.76	0.07	21.99	45.59	10.19	74.72	0.15	0.33	5.56	0.80	0.12
21	62.58	36.44	6.41	0.81	3.59	9.20	12.20	3.00	0.46	14.55	5.53	23.76
22	2.41	3.75	75.56	0.75	7.25	83.63	29.60	9.04	2.43	25.87	6.70	4.16
23	6.02	10.21	74.05	22.72	14.56	4.48	1.95	8.60	7.71	6.44	32.54	6.34
24	5.32	0.83	12.74	3.40	16.41	9.53	4.77	1.28	7.65	0.62	41.37	7.64
25	0.61	3.93	22.26	1.47	15.75	1.32	27.53	16.54	13.52	2.00	0.60	3.22
26	0.60	28.11	2.63	2.02	20.47	2.29	32.25	2.17	27.89	3.31	6.17	5.90
27	11.29	12.19	3.73	32.34	15.59	10.78	88.80	7.85	7.02	12.04	10.91	0.02
28	1.34	18.63	18.11	14.40	8.07	7.56	7.46	0.14	92.24	4.97	7.56	33.73
29	3.30	2.58	1.13	4.12	27.69	22.86	2.65	52.60	6.83	0.05	18.09	52.36
30	14.20	1.55	0.95	0.55	3.86	4.66	98.92	0.06	3.59	34.00	1.72	4.97
31	15.06	5.49	2.45	2.90	18.95	7.70	63.55	0.83	44.42	0.01	6.43	2.44
32	2.01	23.88	0.17	2.07	37.70	12.65	7.17	20.62	11.92	1.50	43.30	9.62
33	0.12	21.92	0.46	5.25	38.19	4.36	15.10	0.26	0.49	46.59	12.52	1.98
34	19.87	1.29	2.95	16.08	13.21	6.85	1.37	0.22	1.70	56.64	16.60	1.10
35	6.17	7.34	22.78	93.35	43.79	55.76	0.83	0.67	14.85	2.82	0.01	12.56
36	6.46	15.95	43.97	87.93	11.07	9.04	5.98	1.57	8.23	3.23	7.52	27.49
37	5.98	5.76	2.95	10.18	78.89	65.28	54.41	39.53	13.24	0.38	2.52	0.54
38	52.07	0.18	4.18	8.83	21.06	55.51	6.94	0.59	0.54	30.55	12.68	42.80
39	29.06	98.84	3.70	7.56	22.34	6.91	0.39	17.98	1.75	8.08	3.05	8.28
40	34.01	1.10	0.53	10.84	79.27	76.05	17.50	3.09	10.08	0.82	8.76	95.56
41	5.16	1.74	17.39	1.04	5.74	5.14	94.32	35.00	2.89	4.21	0.42	17.52
42	0.79	17.78	0.08	97.74	48.09	1.32	1.90	3.86	6.35	22.19	2.89	6.68
43	3.64	7.13	52.75	9.73	8.32	7.16	0.05	5.96	8.19	84.82	6.06	9.89
44	14.79	27.42	16.20	88.35	0.40	1.58	19.09	5.05	61.78	1.63	15.54	7.00
45	2.49	5.86	3.45	0.60	93.18	1.33	0.00	9.26	95.29	39.55	0.80	31.54
46	12.17	6.91	17.25	6.68	3.22	69.12	0.01	1.46	1.11	10.38	26.98	9.20
47	11.08	2.10	9.90	5.52	3.79	9.36	20.96	2.61	0.70	0.90	0.75	14.01
48	9.00	1.69	3.99	1.37	8.78	19.35	13.55	18.83	95.94	12.88	17.02	49.81
49	9.68	27.48	5.49	20.55	2.05	2.88	31.47	8.80	31.90	10.39	0.83	25.79
50	4.68	10.75	18.30	9.37	16.16	43.87	11.10	1.36	2.88	49.91	3.96	17.50
Mean/side	11.70	14.66	13.58	14.06	22.28	16.87	20.85	9.16	21.57	14.63	11.32	18.55
Mean/animal												
Mean/dose		13.32			17.74			17.19			14.83	

Test item.	MNING		Organ		STOMACH	
	20 mg/kg/day (x1)		Treatment:		26/09/2007	
	6534		6532		6531	
Animal N°	217 A	217 B	217 C	218 A	218 B	218 C
Slide No. BC-07-	A1	A2	A3	F1	F2	F3
File No. BC-07-13	A1.xls	A2.xls	A3.xls	F1.xls	F2.xls	F3.xls
No. of cell	% DNA in tail		% DNA in tail		% DNA in tail	
1	39.73	59.39	38.97	77.83	82.86	54.16
2	73.76	13.84	37.33	30.09	1.10	7.52
3	91.30	29.11	15.05	9.39	4.59	14.76
4	94.56	15.00	93.52	3.06	66.64	21.52
5	82.26	84.95	68.76	49.55	66.01	13.49
6	38.34	52.65	92.41	55.15	0.12	23.18
7	47.07	29.42	47.94	61.77	49.72	29.98
8	5.24	24.88	51.19	84.14	30.10	8.18
9	9.24	84.71	52.85	8.71	20.29	5.86
10	12.77	83.31	80.07	29.77	23.70	8.31
11	86.50	89.22	0.53	3.25	64.81	14.45
12	61.68	75.79	20.96	67.25	34.07	9.97
13	76.86	62.22	89.54	27.10	2.82	26.83
14	25.67	31.69	86.73	75.37	33.54	4.90
15	0.15	88.12	16.26	3.45	9.07	5.20
16	16.09	87.02	55.07	12.57	64.54	7.66
17	47.65	55.43	63.60	3.33	20.66	20.90
18	70.30	88.31	87.02	93.52	53.26	0.05
19	14.42	77.04	86.12	73.49	6.21	16.99
20	85.27	73.74	67.53	48.33	26.88	17.53
21	87.47	54.54	27.82	21.85	3.35	2.11
22	73.70	94.50	5.96	90.58	25.46	18.98
23	0.00	56.72	74.28	0.16	85.27	10.20
24	31.22	52.38	41.45	22.60	42.36	0.47
25	69.87	29.98	3.90	71.56	46.53	4.89
26	12.99	90.16	79.73	0.25	82.01	5.82
27	16.63	2.57	86.23	1.53	6.08	3.70
28	59.04	30.76	42.86	57.24	35.33	43.98
29	16.58	59.80	62.53	1.71	40.90	0.41
30	73.12	53.64	81.30	0.14	74.37	2.12
31	94.03	0.39	90.84	73.05	16.21	8.39
32	86.54	84.54	69.45	47.32	24.55	3.25
33	86.98	91.02	75.89	50.07	11.80	0.94
34	96.42	74.12	72.74	5.04	3.81	1.77
35	18.15	31.80	0.88	76.63	91.03	0.08
36	14.79	91.42	16.73	14.17	49.27	0.00
37	12.82	2.86	84.35	3.70	0.00	2.27
38	8.60	39.25	5.98	9.47	2.17	1.69
39	26.67	38.00	38.94	27.50	11.15	13.52
40	78.55	14.74	3.69	21.28	82.49	2.15
41	87.85	20.79	31.40	15.66	83.80	3.69
42	13.59	11.98	32.44	15.66	80.27	8.40
43	15.60	12.50	83.10	18.91	62.81	0.36
44	79.33	30.63	50.34	72.71	42.97	0.20
45	84.56	52.43	64.23	44.14	26.76	1.56
46	74.89	54.01	40.60	46.15	49.21	8.33
47	54.57	37.04	65.16	1.31	50.23	2.45
48	25.30	84.66	91.80	4.91	45.40	10.92
49	43.97	68.69	16.60	84.88	52.51	17.92
50	76.76	15.42	10.18	1.31	50.23	0.44
Mean/slide	49.99	51.74	52.05	35.58	43.50	2.32
Mean/animal	49.99	51.74	52.05	35.58	43.50	2.32
Meandose	49.99	51.74	52.05	35.58	43.50	2.32

## Appendix No. 10: Individual values for Nuclei's OTM / DUODENUM

Test item	Dose.	Distilled water			Organ:	DUODENUM			1 <sup>st</sup> treatment			25/09/2007			26/09/2007		
		0 mg/kg/day (x2)															
Animal N°	Slide No. BC-07-14	6512			No. of cell	6514			No. of cell	6511			No. of cell	6515			
		232 A	232 B	232 C		233 A	233 B	233 C		234 A	234 B	234 C		235 A	235 B	235 C	
File No. BC-07-14	Q1.xls	Q2.xls	Q3.xls	Q1.xls	K1.xls	K2.xls	K3.xls	D1.xls	D2.xls	D3.xls	O1.xls	O2.xls	O3.xls				
		Olive TailMoment			Olive TailMoment			Olive TailMoment			Olive TailMoment						
1	0.58	11.27	1.29	0.71	7.51	0.47	17.37	38.97	14.65	2.86	0.00	0.02	28.81				
2	11.56	18.43	0.71	0.71	1.16	0.21	0.39	17.37	42.94	0.84	9.63	0.92	0.02				
3	2.78	0.04	0.00	0.00	0.12	2.51	3.78	40.99	10.42	0.00	0.05	0.12	26.38				
4	22.80	0.15	1.71	4.92	8.24	26.58	0.05	32.15	25.47	9.55	0.00	0.03	11.73				
5	16.77	0.37	7.18	7.18	4.26	0.18	12.35	18.64	4.18	6.02	1.28	6.44	0.87				
6	19.84	0.07	7.18	7.18	0.68	0.03	4.22	11.63	10.14	0.00	27.90	22.64	0.01				
7	27.99	0.66	0.06	0.06	5.67	0.70	3.20	37.94	0.00	1.56	0.00	0.01	19.51				
8	0.45	0.10	0.67	0.67	0.16	14.10	7.40	30.82	0.18	1.67	0.01	0.14	4.83				
9	0.09	5.49	0.07	0.07	3.28	13.30	0.01	10.07	9.68	2.00	4.03	21.32	0.01				
10	0.01	2.79	0.03	0.03	20.87	1.51	2.66	1.29	2.05	45.72	18.19	0.08	0.34				
11	14.84	1.19	3.64	0.14	0.16	0.23	7.04	0.59	1.25	1.39	0.83	0.27	0.03				
12	2.92	0.02	0.14	0.14	0.06	4.68	0.01	24.99	14.33	4.53	0.09	0.00	0.00				
13	1.17	0.22	0.16	0.16	6.32	0.66	2.90	19.26	0.00	0.01	1.14	3.87	0.68				
14	1.92	0.00	0.98	0.98	26.02	19.60	0.00	0.88	0.13	28.64	7.17	0.01	0.00				
15	0.00	0.86	5.72	5.72	7.22	19.58	0.01	22.78	0.01	0.03	5.96	17.67	2.87				
16	0.10	2.85	15.63	15.63	0.00	20.49	13.12	45.99	12.45	0.14	0.15	0.09	9.91				
17	0.00	2.97	0.30	0.30	0.08	8.54	0.33	0.00	0.37	13.72	0.06	0.19	0.00				
18	0.01	26.21	5.17	5.17	0.00	0.66	0.21	14.94	4.80	33.26	17.04	1.36	0.09				
19	3.25	1.15	0.05	0.05	2.35	0.00	1.37	0.91	0.87	16.36	0.03	36.67	12.54				
20	0.00	16.97	9.99	9.99	0.00	6.47	0.86	44.03	4.10	17.21	0.01	0.05	0.08				
21	0.00	14.95	0.21	0.21	1.88	0.94	4.84	0.30	10.02	21.30	2.60	0.00	2.33				
22	24.60	2.17	1.82	1.82	0.32	2.94	1.14	22.57	0.16	4.87	23.88	5.62	0.00				
23	1.33	0.07	7.05	7.05	0.00	1.36	4.76	3.12	0.00	0.01	9.53	0.01	0.04				
24	27.26	0.16	2.57	2.57	11.98	6.39	4.39	52.31	0.84	4.43	9.41	34.16	6.43				
25	3.34	0.53	7.86	7.86	0.00	1.84	10.78	31.80	1.08	3.13	0.94	0.02	17.04				
26	8.73	0.27	0.01	0.01	0.02	6.88	0.15	37.80	0.27	0.26	5.02	0.22	0.02				
27	0.05	20.37	1.89	1.89	0.02	1.29	18.34	42.02	0.38	14.20	2.24	0.06	0.00				
28	0.12	1.06	10.42	10.42	7.61	2.27	0.44	0.02	1.86	0.02	18.13	0.05	1.55				
29	0.38	1.07	2.66	2.66	9.32	0.93	2.96	39.41	0.01	11.22	0.00	1.16	0.18				
30	1.01	0.49	5.47	5.47	0.03	0.05	3.35	0.45	1.92	10.67	5.17	7.24	0.01				
31	1.24	9.09	0.40	0.40	0.00	3.77	0.45	44.64	1.12	6.82	1.28	25.57	4.46				
32	1.75	32.92	0.38	0.38	0.42	32.16	16.84	0.30	2.04	12.32	2.05	0.00	0.13				
33	25.95	5.96	0.01	0.01	2.61	2.84	20.24	34.25	5.60	24.80	14.76	4.48	6.41				
34	24.62	1.24	0.00	0.00	16.52	7.18	0.74	19.91	1.24	0.12	0.00	0.29	0.33				
35	4.38	0.01	8.12	8.12	0.04	10.59	0.00	12.55	5.43	0.26	0.09	35.34	0.28				
36	0.00	1.18	0.01	0.01	0.70	0.59	0.02	42.60	0.61	0.07	0.26	1.76	1.10				
37	0.20	2.45	28.67	28.67	0.00	24.72	0.27	0.02	0.10	1.98	1.00	0.07	0.13				
38	13.34	1.33	0.13	0.13	0.02	4.02	0.06	3.45	7.37	4.19	0.69	0.00	1.45				
39	1.29	9.77	37.26	37.26	0.20	8.90	29.49	41.24	0.99	20.00	0.07	0.00	8.34				
40	0.00	0.09	0.74	0.74	0.66	0.37	0.92	9.75	0.05	15.18	1.21	0.31	11.46				
41	14.75	2.19	6.18	6.18	23.61	8.94	0.00	2.55	0.52	21.23	0.20	0.05	10.05				
42	27.45	13.15	27.36	27.36	0.10	0.00	0.70	2.26	10.30	12.71	0.11	0.57	0.00				
43	19.19	0.00	4.06	4.06	0.15	4.55	0.51	4.83	12.02	5.62	0.00	0.00	25.70				
44	1.45	0.14	1.26	1.26	20.70	12.75	0.00	6.96	19.76	7.04	12.76	0.00	5.48				
45	4.19	0.00	0.20	0.20	0.09	2.95	2.99	2.79	4.63	20.34	0.00	7.67	8.91				
46	0.24	14.72	24.77	24.77	0.00	0.06	2.46	9.05	0.00	0.30	0.09	0.00	9.30				
47	0.02	2.91	0.07	0.07	0.07	13.74	0.00	0.00	0.08	6.95	0.40	0.33	6.62				
48	0.23	0.48	2.76	2.76	6.23	22.55	25.66	3.79	7.91	6.21	5.26	0.00	1.99				
49	0.00	0.94	0.67	0.67	0.80	0.67	3.91	3.62	0.00	3.45	17.83	0.21	0.22				
50	0.01	0.87	8.68	8.68	0.28	4.33	2.23	30.23	0.14	1.10	0.00	0.00	0.86				
Median/slide	1.31	1.11	1.77	1.77	0.37	2.94	1.80	12.09	1.56	4.70	0.97	0.20	0.98				
Median/animal	1.25	1.25	1.25	1.25	1.58	1.58	1.58	1.58	1.58	1.58	1.58	0.48	0.48				
Median/dose	1.48	1.48	1.48	1.48	1.48	1.48	1.48	1.48	1.48	1.48	1.48	0.48	0.48				

Test item: Dose:	Animal N° Slide No. BC-07- Code BC-07-14 File No. BC-07-14	CATECHOL 400 mg/kg/day (x2)			DUODENUM		Organ:		1 <sup>st</sup> treatment: 2 <sup>nd</sup> treatment:		25/09/2007 26/09/2007		
		6518			6517		6520		6519				
		239 A H1.xls	239 B H2.xls	239 C H3.xls	240 A M1.xls	240 B M2.xls	240 C M3.xls	241 A S1.xls	241 B S2.xls	241 C S3.xls	242 A N1.xls	242 B N2.xls	242 C N3.xls
No. of cell		Olive tailMoment			Olive tailMoment			Olive tailMoment			Olive tailMoment		
1		0.02	20.44	0.19	0.06	3.19	1.62	22.67	0.29	19.79	5.48	0.10	0.65
2		21.72	3.06	0.22	4.39	5.90	19.37	0.22	1.18	0.01	31.35	10.48	7.52
3		33.11	0.06	3.62	22.89	1.78	1.10	5.65	0.01	2.58	0.07	8.49	17.52
4		16.62	40.35	0.00	11.11	2.49	0.33	0.75	8.45	0.05	2.19	0.14	0.28
5		0.01	9.89	0.01	6.18	1.46	0.73	14.54	2.33	6.01	60.86	26.34	24.78
6		2.76	27.46	7.10	7.70	4.98	0.65	18.33	21.51	0.00	10.89	17.79	0.32
7		9.09	0.28	0.76	26.53	0.60	30.40	0.09	0.01	0.00	63.69	0.09	27.79
8		0.00	35.02	0.00	2.00	2.18	8.12	0.14	0.05	33.60	24.97	0.46	0.03
9		25.62	0.03	0.36	0.92	0.07	26.95	18.06	6.71	0.74	0.19	0.46	3.60
10		22.98	42.04	26.83	13.18	10.71	0.02	8.73	34.38	2.46	0.24	2.60	8.94
11		0.00	0.00	0.00	0.10	6.16	0.69	0.02	6.55	21.90	5.34	10.78	0.21
12		1.07	0.00	0.00	0.43	11.74	0.92	1.28	1.97	0.03	20.50	12.91	2.86
13		0.00	0.00	0.36	14.21	0.51	2.46	0.79	0.01	0.00	1.37	5.30	6.90
14		0.53	5.45	0.00	41.37	13.67	1.18	0.11	1.29	0.00	22.00	0.00	20.87
15		0.00	26.02	0.63	0.20	0.92	10.06	0.36	0.01	0.00	0.16	0.00	1.84
16		1.55	0.00	12.49	1.14	9.73	2.11	0.87	4.02	5.06	0.04	7.10	1.30
17		1.47	24.15	3.07	0.05	2.47	25.36	0.23	0.00	0.00	45.87	8.93	1.25
18		0.13	38.93	6.92	6.06	14.09	0.46	1.38	22.91	0.01	33.37	0.36	0.26
19		0.37	0.41	6.01	32.42	46.17	2.81	1.65	25.70	0.04	8.40	8.64	1.34
20		2.48	0.00	1.35	0.31	1.03	0.02	31.12	0.00	1.49	0.85	30.22	0.15
21		0.00	26.81	0.10	3.12	10.46	2.36	0.02	4.96	0.00	0.11	9.15	2.00
22		36.07	0.00	0.28	20.83	0.36	0.14	0.00	0.99	41.07	0.67	1.37	0.65
23		0.01	37.61	0.05	0.82	0.04	13.06	0.00	8.93	0.08	1.86	2.16	4.16
24		19.22	0.04	0.03	8.94	0.62	3.89	0.11	0.00	0.09	16.56	1.56	0.06
25		7.24	0.03	0.02	0.41	33.80	11.69	0.34	2.86	13.52	3.19	10.83	31.84
26		0.09	1.07	9.35	8.16	7.69	6.25	0.05	0.57	6.01	1.01	10.10	11.02
27		0.91	0.00	0.01	0.00	0.00	0.34	0.01	0.77	0.10	1.01	16.04	0.00
28		5.97	0.01	3.51	0.33	8.23	0.01	11.06	0.00	1.43	22.72	2.57	10.07
29		18.79	0.05	0.00	0.25	5.27	1.29	0.01	0.00	2.21	23.26	1.09	0.50
30		0.19	9.45	5.63	0.23	1.57	3.75	0.00	5.70	0.02	0.08	0.02	0.80
31		17.98	0.23	1.36	4.96	9.30	0.07	32.19	1.86	0.00	9.13	0.09	27.81
32		0.20	9.79	1.37	0.01	0.33	43.05	0.02	0.02	0.00	15.00	0.01	0.50
33		11.45	0.00	10.41	0.30	12.94	0.64	0.17	0.03	0.47	0.20	19.20	0.21
34		0.92	43.65	0.25	0.59	0.27	45.78	7.74	0.01	1.91	1.88	0.30	31.51
35		3.08	0.52	0.90	0.88	14.41	8.95	0.00	5.24	40.08	9.55	1.11	28.19
36		0.33	0.72	21.01	0.80	17.38	23.33	0.01	6.51	5.35	0.61	0.03	1.65
37		0.23	17.74	14.77	0.85	8.39	0.62	0.29	19.10	41.58	25.82	3.18	0.15
38		0.64	4.89	0.00	5.79	9.21	0.20	0.61	3.76	9.97	2.54	0.00	0.26
39		33.97	0.61	24.70	0.02	27.76	1.96	0.00	1.12	15.40	0.01	0.62	0.26
40		0.02	0.34	8.18	2.22	3.85	0.20	27.93	0.32	1.54	0.62	0.27	1.28
41		0.71	0.09	4.66	0.78	8.09	0.00	0.00	34.30	0.03	5.74	0.04	0.22
42		0.93	0.91	0.04	0.40	1.23	1.30	0.00	0.01	16.89	1.71	1.34	0.20
43		0.07	22.99	19.69	0.28	25.95	20.75	12.63	0.03	23.10	11.42	0.21	40.13
44		3.55	3.19	39.36	0.76	24.23	2.90	0.00	45.04	0.00	31.23	0.03	0.30
45		0.00	35.92	0.51	2.75	33.43	0.08	0.00	0.00	0.00	0.22	0.28	0.02
46		0.15	0.41	45.43	17.31	1.15	1.38	0.00	0.06	24.14	2.67	0.15	28.22
47		0.05	0.11	1.08	0.07	1.21	4.72	0.00	9.38	0.09	8.23	0.03	22.48
48		33.78	0.00	0.17	2.17	9.67	0.18	0.00	3.05	0.16	4.60	0.92	0.05
49		2.03	0.46	8.15	0.00	9.78	0.42	0.01	10.41	27.41	1.53	0.10	1.04
50		0.00	12.25	1.02	6.90	12.38	2.41	30.58	0.00	0.08	6.60	33.78	0.01
Median/slide		0.91	0.66	0.96	0.87	6.03	1.50	0.20	1.57	0.60	3.89	1.10	1.27
Median/animal			0.90			2.18			0.59			1.60	
Median/dose							1.28						

Test item. Dose:	CATECHOL 200 mg/kg/day (x2)			Organ:	DUODENUM		1 <sup>st</sup> treatment: 2 <sup>nd</sup> treatment		25/09/2007 26/09/2007			
	6524				6521		6522		6525			
Animal N°	243 A	243 B	243 C	244 A	244 B	244 C	245 A	245 B	245 C	246 A	246 B	246 C
Slide No. BC-07-	A1	A2	A3	P1	P2	P3	L1	L2	L3	E1	E2	E3
Code BC-07-14	A1.xls	A2.xls	A3.xls	P1.xls	P2.xls	P3.xls	L1.xls	L2.xls	L3.xls	E1.xls	E2.xls	E3.xls
File No. BC-07-14	A1.xls	A2.xls	A3.xls	P1.xls	P2.xls	P3.xls	L1.xls	L2.xls	L3.xls	E1.xls	E2.xls	E3.xls
No. of cell	Olive tailMoment			Olive tailMoment			Olive tailMoment			Olive tailMoment		
1	0.38	0.07	2.38	0.59	3.50	29.59	33.83	22.21	26.21	19.61	0.00	15.30
2	13.03	0.03	19.60	0.00	0.02	4.87	29.07	9.45	14.91	47.12	0.11	1.05
3	3.89	2.65	0.84	47.33	0.05	19.46	33.53	10.56	23.55	5.38	0.02	19.65
4	0.22	3.55	9.49	19.93	0.10	15.62	7.21	0.77	2.27	1.57	0.22	18.26
5	0.00	2.76	0.51	1.34	0.96	0.31	44.43	3.35	3.81	0.37	27.24	7.41
6	5.06	0.03	8.97	3.87	19.29	17.51	0.01	6.78	20.21	2.32	18.54	8.05
7	31.70	0.05	0.01	7.58	0.05	0.00	11.96	14.50	6.73	0.15	5.59	8.71
8	4.78	0.04	3.41	28.11	0.81	8.97	19.63	0.27	0.00	6.05	6.65	1.49
9	0.07	3.22	0.49	27.70	25.32	0.00	11.72	0.01	8.19	10.72	1.04	0.42
10	4.35	1.52	6.73	0.12	0.65	18.10	0.19	16.90	0.18	9.47	2.13	1.10
11	28.29	0.15	0.83	15.54	36.72	6.22	30.16	0.27	12.62	0.11	0.28	0.03
12	1.37	0.00	18.37	0.01	55.50	0.21	0.77	16.84	7.62	0.22	0.46	20.56
13	1.24	0.01	8.15	21.57	8.21	20.14	0.36	1.47	1.27	5.04	0.61	2.05
14	6.52	0.22	30.74	3.08	13.11	18.62	47.99	14.67	23.67	0.00	0.00	26.18
15	3.01	0.05	0.00	4.26	0.01	0.18	21.20	1.47	0.01	1.18	4.23	8.01
16	0.60	7.00	0.01	16.76	0.92	15.95	25.91	5.16	20.58	0.00	0.00	1.40
17	0.00	1.30	16.34	8.20	3.82	0.00	16.52	1.61	4.64	3.99	13.56	0.01
18	2.57	1.12	19.09	0.74	0.20	5.01	0.65	0.35	2.16	12.70	1.20	0.89
19	0.59	1.02	0.11	0.45	0.10	11.44	24.61	22.07	3.30	4.20	11.41	5.54
20	0.50	0.20	1.55	2.70	12.77	0.22	16.90	4.54	4.34	8.88	0.00	12.34
21	13.51	34.09	0.02	0.02	0.04	10.23	44.30	7.96	0.24	0.69	0.20	0.01
22	7.17	0.46	0.00	1.97	0.00	9.66	2.95	3.99	0.00	10.30	0.62	2.30
23	8.62	0.47	4.77	0.11	1.56	0.00	30.82	3.03	0.12	7.71	3.07	0.03
24	0.01	1.90	38.08	4.34	4.66	9.31	5.09	0.93	0.39	0.06	12.30	9.33
25	3.89	0.72	0.00	0.60	0.39	0.05	0.00	3.04	4.36	0.00	5.61	19.65
26	3.18	6.90	1.13	7.82	3.62	1.25	24.90	0.76	3.78	5.48	3.94	4.30
27	12.60	0.14	43.28	1.16	0.00	0.00	25.70	0.02	4.90	6.95	0.07	0.26
28	0.27	0.00	0.80	3.68	6.93	12.10	14.77	1.54	23.48	6.33	0.08	3.20
29	0.11	3.21	4.67	27.45	37.94	0.14	5.94	7.03	6.58	1.20	25.04	0.74
30	0.94	1.41	3.09	12.39	7.17	0.56	3.05	0.36	8.19	0.04	0.50	16.12
31	0.00	0.00	17.11	4.70	0.11	8.24	4.52	0.54	11.90	0.43	16.24	7.24
32	0.68	0.00	14.81	0.00	0.87	8.08	1.17	4.44	8.87	7.43	19.34	10.15
33	2.84	0.13	15.45	13.76	2.42	4.31	12.08	3.17	33.07	5.11	0.04	22.90
34	42.44	1.39	0.00	0.06	0.18	0.42	0.55	7.00	9.88	4.82	0.01	9.91
35	16.74	0.86	1.40	6.23	0.01	1.11	1.65	1.16	14.39	0.96	3.75	0.91
36	12.42	0.23	1.29	15.22	5.02	7.93	3.68	2.57	12.01	0.69	2.30	19.15
37	2.91	0.00	24.38	2.97	0.12	1.88	22.86	10.05	29.88	7.26	1.63	3.42
38	0.57	11.68	11.24	0.92	0.09	0.10	23.55	38.57	9.07	0.00	1.24	11.37
39	32.79	10.39	2.13	24.05	7.72	0.30	2.62	19.51	0.01	39.96	5.27	18.73
40	6.00	0.91	20.45	2.28	0.41	1.13	28.45	8.23	25.26	5.26	1.66	26.77
41	21.04	1.46	0.00	0.00	5.58	5.02	0.02	7.42	7.25	23.20	1.36	6.78
42	9.92	1.03	0.08	1.59	0.85	6.03	23.52	11.47	7.21	39.26	0.42	13.00
43	13.01	5.93	1.00	0.46	32.08	6.51	5.40	0.33	1.35	49.15	5.78	1.73
44	30.89	8.49	1.97	3.94	0.71	0.08	16.91	0.90	1.71	1.30	1.59	5.85
45	46.62	0.13	2.26	2.19	0.72	1.39	5.75	10.67	5.01	32.63	0.03	15.51
46	10.18	0.01	0.00	2.31	0.61	0.56	0.70	4.87	3.79	26.26	0.78	8.56
47	15.34	16.12	0.63	2.64	0.30	2.29	2.25	20.49	4.28	22.52	5.29	2.57
48	5.41	0.03	0.05	0.54	0.14	2.07	0.31	20.49	11.86	21.51	30.29	4.33
49	36.65	3.70	0.62	3.59	0.10	0.13	37.91	28.54	6.21	0.58	5.98	3.63
50	0.46	0.03	0.33	23.05	1.35	3.98	0.14	0.91	12.28	1.41	12.89	22.55
Median/slide	4.12	0.79	1.76	3.03	0.83	3.14	11.84	4.22	6.65	5.07	1.61	7.01
Median/animal		1.43			2.23			6.07			4.21	

Test item: Dose:	Organ:	DUODENUM		1 <sup>st</sup> treatment:		25/09/2007		26/09/2007		6530						
		CATECHOL 100 mg/kg/dav (x2)		6529		6526		6525		6524						
		Animal N°	Slide No. BC-07-Code BC-07-14	File No. BC-07-14	No. of cell	247 A	247 B	247 C	248 A	248 B	248 C	249 A	249 B	249 C	250 A	250 B
		G1	G2	G3	I1	I2	I3	R1	R2	R3	B1	B2	B3	B1.xls	B2.xls	B3.xls
		Olive tailMoment			Olive tailMoment			Olive tailMoment			Olive tailMoment			Olive tailMoment		
1		33.72	33.52	10.59	33.20	0.80	9.37	17.34	6.27	7.64	2.70	17.87	1.54			
2		33.34	14.84	6.71	47.40	55.13	1.18	19.66	0.00	10.97	52.87	3.82	8.51			
3		46.42	0.64	10.72	21.53	28.97	2.36	0.11	14.85	0.20	0.05	9.29	6.72			
4		2.65	4.66	10.22	0.49	18.62	0.94	3.31	2.59	3.25	0.67	12.53	1.20			
5		27.93	1.64	2.75	7.06	33.57	12.02	43.53	0.03	15.76	3.81	0.17	0.00			
6		50.87	1.27	13.37	1.94	0.19	0.00	14.04	28.69	0.13	29.11	36.95	2.65			
7		1.71	32.05	8.29	29.67	4.34	14.61	0.28	21.44	0.44	0.54	10.70	26.84			
8		44.51	10.76	22.03	0.13	27.46	0.60	25.62	8.61	33.94	42.13	14.50	2.11			
9		23.93	0.19	14.57	31.95	4.52	37.48	52.48	0.39	3.44	0.01	3.51	3.64			
10		41.99	2.22	8.85	2.10	5.23	0.49	42.57	0.46	0.36	4.54	8.02	13.36			
11		33.64	13.57	0.48	1.28	1.85	0.36	2.22	0.93	1.43	2.23	0.17	5.51			
12		40.82	29.25	4.07	4.65	11.46	1.64	17.42	3.50	2.24	26.93	1.53	15.19			
13		47.94	20.83	6.64	39.01	37.41	1.94	46.53	5.18	0.22	0.00	6.51	9.45			
14		54.47	1.81	1.57	56.75	0.01	7.28	7.65	8.62	0.00	7.54	2.84	0.06			
15		23.26	0.55	17.24	40.96	33.20	2.83	22.93	0.98	0.00	6.26	0.01	11.53			
16		20.17	4.52	11.87	6.91	5.08	0.05	26.40	0.09	6.67	0.25	1.94	3.47			
17		3.56	4.15	0.55	13.24	0.73	6.48	12.82	13.42	1.02	12.46	2.85	2.31			
18		15.03	10.58	1.77	0.09	32.14	0.04	7.93	8.32	0.01	0.07	6.76	7.49			
19		2.72	41.66	0.27	0.43	24.02	29.85	12.98	0.00	5.98	0.21	2.02	0.00			
20		11.80	17.95	17.95	7.31	14.42	14.33	26.15	18.78	1.08	5.33	0.01	7.59			
21		21.62	32.89	10.46	67.65	5.76	1.86	3.38	30.90	2.31	0.06	2.30	0.00			
22		47.27	29.75	3.97	45.20	9.54	15.11	23.63	9.22	2.45	0.00	0.42	5.90			
23		42.27	0.04	42.66	0.81	35.42	6.78	2.53	0.33	2.46	3.59	7.24	7.59			
24		9.94	30.38	33.61	58.58	0.52	3.45	37.24	3.82	4.80	16.66	13.23	0.47			
25		22.32	0.04	5.24	1.78	15.32	27.85	0.00	6.51	2.65	0.02	1.58	0.27			
26		52.31	48.97	16.49	34.91	0.74	3.39	1.20	15.42	1.59	5.82	10.96	5.10			
27		11.13	18.94	21.63	2.65	0.00	25.00	0.60	23.25	0.06	0.01	1.72	16.81			
28		4.59	1.96	0.09	34.44	0.00	0.00	24.73	0.62	4.98	1.01	2.22	0.00			
29		7.09	15.71	1.49	0.85	0.00	4.87	23.26	6.37	1.25	0.05	5.83	1.40			
30		25.51	0.06	0.41	46.38	2.50	4.08	34.66	16.50	1.56	7.29	3.15	4.12			
31		2.99	0.18	2.48	21.56	17.50	0.03	0.42	2.15	0.44	0.05	1.91	0.37			
32		0.63	3.44	0.26	13.59	2.96	16.93	4.95	0.96	2.72	0.68	0.39	5.27			
33		10.64	13.05	26.71	27.99	3.69	42.19	4.63	9.41	0.08	2.36	0.97	3.85			
34		3.32	0.00	3.92	11.37	0.00	11.09	9.11	0.77	0.00	0.00	0.06	6.57			
35		0.57	4.92	12.92	17.23	0.10	0.02	7.87	0.50	7.02	0.43	1.35	3.50			
36		34.89	9.51	16.94	0.29	8.45	0.23	3.04	16.03	1.70	0.00	0.00	0.51			
37		7.41	27.28	16.53	15.63	0.88	37.58	0.25	7.10	1.20	10.03	1.83	0.04			
38		41.20	0.02	0.00	0.01	0.00	18.33	0.16	17.13	0.02	0.14	1.71	14.33			
39		45.56	15.70	4.19	24.68	0.73	22.28	18.72	0.00	4.22	0.04	0.01	0.79			
40		1.78	28.86	4.85	26.96	14.02	13.36	28.68	19.44	1.07	1.09	0.00	2.87			
41		0.07	35.81	0.00	4.55	29.96	4.70	0.62	11.68	1.22	0.10	0.02	0.43			
42		36.09	3.62	27.35	43.03	10.93	0.02	4.27	0.00	2.83	16.81	0.00	0.13			
43		56.97	1.27	2.90	20.61	29.33	26.85	5.02	0.06	0.01	18.15	0.41	4.67			
44		3.15	3.38	5.08	8.55	7.29	1.29	11.31	0.08	1.07	13.23	0.06	0.00			
45		2.76	0.24	0.97	5.88	1.38	25.22	8.95	3.73	1.01	11.48	0.02	14.68			
46		11.96	8.17	0.12	36.91	9.20	16.52	3.20	0.40	0.08	7.02	8.54	4.87			
47		0.00	2.66	10.89	2.49	0.16	36.42	0.05	7.37	0.52	17.95	2.61	6.40			
48		51.12	7.11	3.52	6.68	4.00	9.96	5.24	0.05	0.49	1.00	18.94	1.60			
49		1.54	9.04	1.08	25.37	0.59	9.35	0.36	0.14	0.13	1.93	0.49	6.70			
50		25.85	25.14	8.26	1.45	19.99	20.84	12.92	1.33	0.61	27.38	4.41	6.09			
Median/slide		21.97	7.64	5.94	13.42	5.16	6.63	8.44	3.78	1.21	2.08	1.98	3.74			
Median/animal			9.73			7.29			3.12			2.49				
Median/dose						4.54										

Test item: Dimethylhydrazine  
Dose: 20 mg/kg/day (x1)

Organ: DUODENUM  
Treatment: 26/09/2007

Animal N°	236 A	236 B	236 C	237 A	237 B	237 C	238 A	238 B	238 C
Slide No. BC-07-14	J1	J2	J3	F1	F2	F3	C1	C2	C3
File No. BC-07-14	J1.xls	J2.xls	J3.xls	F1.xls	F2.xls	F3.xls	C1.xls	C2.xls	C3.xls
No. of cell	3088	2438	1182	4061	2398	2896	000	2014	3355
1	23.00	8.27	3.18	41.88	15.74	8.26	30.73	1.30	1.30
2	14.10	8.98	33.07	18.21	1.58	8.17	49.55	4.82	0.61
3	23.86	8.10	0.93	13.35	13.41	0.71	14.15	1.45	2.13
4	46.12	11.69	18.42	21.14	22.49	37.53	20.09	37.22	11.82
5	4.33	9.46	18.33	2.77	2.91	43.50	4.32	5.78	5.43
6	35.11	2.37	3.80	13.25	3.50	16.59	36.56	6.90	25.35
7	37.14	0.13	20.94	17.05	14.67	6.40	23.63	1.25	0.00
8	5.46	23.53	24.01	16.25	31.22	14.39	19.31	25.62	7.54
9	10.33	23.35	2.32	3.53	39.37	4.36	4.58	0.33	5.38
10	8.82	12.29	1.82	6.91	15.69	14.02	11.31	0.75	24.19
11	6.75	9.49	9.90	37.77	14.51	6.08	3.18	3.10	22.83
12	22.25	6.90	15.91	9.58	6.47	12.81	6.63	7.94	0.62
13	3.05	6.15	46.35	19.12	6.21	0.34	1.70	15.09	2.40
14	8.90	37.77	10.06	33.64	3.68	3.24	20.30	24.53	6.07
15	42.76	10.70	16.13	24.37	2.81	38.30	5.07	2.04	6.96
16	28.14	4.87	14.69	46.75	2.91	33.20	3.80	3.51	43.05
17	5.58	1.82	2.09	11.75	2.14	1.30	11.55	4.13	9.34
18	18.56	0.85	12.19	7.34	22.23	1.91	3.21	0.29	19.18
19	47.75	6.35	3.83	21.90	4.67	0.45	2.86	3.29	28.05
20	46.82	11.05	36.62	16.89	3.51	10.37	3.92	2.75	36.20
21	6.13	5.04	6.47	32.83	7.90	18.84	3.58	3.77	36.80
22	4.49	3.76	1.79	12.97	66.02	51.48	6.14	1.37	14.72
23	4.27	37.65	5.49	4.97	5.43	2.73	13.69	2.95	28.05
24	3.89	23.13	7.55	25.64	48.94	45.53	12.70	18.90	4.65
25	2.02	31.60	25.24	24.53	0.28	22.79	5.36	1.96	6.62
26	49.05	6.06	49.44	12.81	0.53	13.14	27.83	0.41	23.78
27	15.25	28.11	18.78	23.81	4.90	0.63	6.73	2.66	26.97
28	8.90	6.87	2.43	40.35	11.03	29.83	27.95	10.95	6.24
29	6.17	29.33	1.08	5.24	0.92	28.59	2.62	1.50	8.09
30	6.53	42.08	1.58	0.09	1.48	18.48	26.78	40.72	21.11
31	0.60	49.59	5.97	4.38	1.66	8.19	6.73	6.82	25.26
32	5.39	52.13	35.90	11.35	3.40	8.89	15.20	13.26	11.17
33	11.65	4.66	29.27	1.00	0.55	5.77	0.00	1.99	17.37
34	9.28	32.80	19.20	4.05	14.98	40.43	14.03	0.56	40.73
35	29.97	23.31	18.90	1.09	35.26	1.16	5.79	26.32	49.02
36	1.00	5.20	10.58	2.80	30.74	0.63	8.28	4.02	37.25
37	35.54	6.64	4.96	19.58	9.00	25.93	8.34	10.74	2.99
38	0.93	20.77	7.93	16.51	1.66	4.56	10.14	2.02	0.31
39	12.32	14.94	6.89	1.82	0.87	6.23	18.26	0.73	32.94
40	0.97	4.37	1.98	7.35	7.44	8.50	3.04	9.83	31.37
41	21.63	33.98	23.09	22.45	44.70	13.35	15.34	12.85	0.24
42	6.23	12.40	15.15	26.55	1.66	21.10	7.91	8.11	0.92
43	8.88	5.59	6.11	28.03	36.01	0.01	4.38	14.88	35.25
44	29.17	29.68	7.46	4.46	5.82	34.58	2.46	11.29	2.16
45	2.72	2.02	13.40	15.56	10.92	26.81	26.00	47.68	28.63
46	4.33	4.01	12.26	13.72	12.96	7.85	1.94	7.20	20.03
47	1.19	1.03	6.43	14.80	36.47	3.48	5.34	7.96	2.59
48	1.39	8.57	33.52	47.05	10.59	7.33	1.17	0.23	1.50
49	1.72	8.39	11.93	6.41	14.17	1.90	28.68	40.59	23.32
50	8.89	9.22	11.20	15.18	6.95	8.70	7.32	4.48	13.27
Median/slide	8.89	9.22	11.20	15.18	6.95	8.70	7.32	4.48	13.27
Median/animal		9.37		11.19	8.94			7.37	
Median/dose									

## Appendix No. 11: Individual values for Tail length / DUODENUM

Test item: Dose.	Animal N°	Distilled water 0 mg/kg/day (x2)				Organ	DUODENUM				1 <sup>st</sup> treatment: 2 <sup>nd</sup> treatment		25/09/2007 26/09/2007		6515			
		6512		6514			6511		6515		234 B		234 C		235 B		235 C	
		Slide No. BC-07-14	File No. BC-07-14	Q1.xls	Q2.xls		Q3.xls	Q3.xls	Q3.xls	K1.xls	K2.xls	K3.xls	K3.xls	D1.xls	D2.xls	D3.xls	O1.xls	O2.xls
No. of cell																		
1	1	23.27	104.35	78.08	67.57	60.06	98.10	93.84	98.10	89.34	24.77	15.01	98.09					
2	2	83.33	93.84	42.04	41.29	22.52	45.79	99.85	110.36	42.04	68.32	45.04	13.51					
3	3	56.31	15.01	13.51	36.79	59.31	87.09	104.35	72.07	14.26	23.27	47.30	96.09					
4	4	93.09	26.28	41.29	92.34	85.58	10.51	117.87	135.88	77.33	9.01	32.28	73.57					
5	5	78.08	24.02	87.84	73.57	36.04	107.36	93.09	81.83	85.58	42.04	75.82	35.28					
6	6	78.08	21.77	72.82	23.27	51.05	67.57	78.83	60.06	12.76	78.83	96.09	13.51					
7	7	90.84	39.79	42.79	60.06	33.78	39.79	96.09	8.26	39.79	10.51	24.77	71.32					
8	8	39.04	21.77	20.27	30.03	82.58	84.83	97.60	27.78	30.03	24.77	51.80	60.06					
9	9	23.27	98.35	38.29	78.83	81.83	22.52	87.09	82.58	39.79	44.29	95.34	15.01					
10	10	23.27	72.82	16.52	86.33	40.54	69.07	51.05	70.57	132.88	66.06	26.28	47.30					
11	11	95.34	47.30	50.30	29.28	30.03	86.33	38.29	52.55	30.78	23.27	36.04	20.27					
12	12	35.28	17.27	33.03	27.03	95.34	23.53	99.85	100.60	63.61	13.51	12.01	15.77					
13	13	27.03	54.80	27.03	61.56	42.04	82.58	94.59	9.76	100.60	28.53	54.80	35.28					
14	14	67.57	11.26	39.04	75.07	105.85	12.76	35.28	14.26	103.60	66.82	21.77	14.26					
15	15	27.03	33.78	48.05	69.07	86.33	22.52	84.83	19.52	12.76	55.55	44.29	70.57					
16	16	35.28	83.33	72.07	23.27	96.09	96.85	130.63	84.08	18.77	15.01	20.27	69.82					
17	17	12.76	98.35	14.26	53.30	102.10	16.52	12.01	12.76	41.29	18.77	46.55	12.76					
18	18	23.27	108.86	42.79	10.51	54.80	25.53	56.31	47.30	118.62	69.82	69.07	11.26					
19	19	46.55	57.06	27.03	67.57	13.51	37.54	65.31	24.77	95.34	35.28	96.09	90.84					
20	20	25.53	103.60	66.06	10.51	96.09	40.54	119.37	44.29	77.33	12.76	22.52	35.28					
21	21	11.26	98.35	14.26	42.04	34.53	65.31	51.80	93.84	107.36	62.31	15.77	87.57					
22	22	76.58	51.80	22.52	25.53	77.33	24.77	93.84	17.27	38.29	94.59	51.80	12.01					
23	23	42.79	17.27	42.04	12.01	30.03	76.58	46.55	6.01	11.26	12.01	99.10	18.02					
24	24	76.58	17.27	28.53	63.06	89.34	78.83	138.89	32.28	64.56	85.58	116.36	84.08					
25	25	55.55	23.27	50.30	16.52	86.33	86.33	84.83	41.29	69.07	30.03	27.78	71.32					
26	26	59.31	26.28	14.26	13.51	63.61	24.02	103.60	24.02	35.28	54.05	51.05	14.26					
27	27	14.26	87.09	26.28	17.27	44.29	87.84	98.35	33.78	81.83	37.54	33.03	15.01					
28	28	16.52	30.78	39.79	72.07	63.06	35.28	20.27	72.78	12.76	69.07	13.51	37.54					
29	29	21.02	46.55	32.28	75.07	51.05	23.27	11.86	12.76	72.82	12.01	48.05	34.53					
30	30	21.77	40.54	50.30	11.26	28.53	54.80	19.52	54.05	74.32	83.33	81.83	15.01					
31	31	31.53	124.62	28.53	12.01	57.06	18.02	138.89	24.77	63.61	60.81	102.10	47.30					
32	32	42.79	110.36	19.52	21.02	110.36	87.84	13.51	42.79	71.32	40.54	9.76	16.52					
33	33	102.10	78.83	15.01	66.06	45.79	107.36	99.10	51.05	100.60	80.33	48.80	61.56					
34	34	101.35	27.03	15.77	79.58	61.56	24.02	90.84	65.31	32.28	10.51	18.77	30.78					
35	35	87.09	16.52	118.62	27.03	112.61	15.01	60.81	39.04	50.30	18.02	105.10	31.53					
36	36	24.77	57.06	14.26	26.28	34.53	21.02	96.85	58.56	21.02	18.02	66.06	33.78					
37	37	44.29	96.85	146.39	13.51	108.11	38.29	16.52	30.78	68.32	51.80	15.77	36.04					
38	38	79.58	63.06	33.78	27.78	101.35	21.02	51.05	65.31	90.09	34.53	12.76	34.53					
39	39	63.61	109.61	113.36	14.26	115.61	94.59	120.87	31.53	103.60	24.77	26.28	88.59					
40	40	25.53	45.79	39.79	54.80	36.04	28.53	50.30	12.76	89.34	61.56	38.29	77.33					
41	41	72.82	66.82	69.82	83.33	65.31	13.51	29.28	43.54	97.60	12.01	31.53	57.81					
42	42	78.08	107.36	123.87	12.76	14.26	48.05	45.04	38.29	94.59	15.01	28.53	14.26					
43	43	88.59	17.27	68.32	13.51	53.30	42.04	51.05	96.85	65.31	12.76	11.26	87.84					
44	44	36.04	45.79	36.04	90.09	90.84	16.52	66.06	110.36	78.08	57.06	12.01	60.81					
45	45	39.79	12.01	15.01	12.01	60.81	55.55	80.33	40.54	97.60	10.51	83.33	75.82					
46	46	15.01	99.10	120.12	21.02	27.03	29.28	73.57	9.76	22.52	24.02	26.28	66.06					
47	47	15.01	60.81	18.02	12.01	27.03	29.28	11.26	14.26	63.61	18.02	21.02	57.81					
48	48	27.78	23.27	75.07	62.31	92.34	117.87	70.57	54.05	78.08	65.31	12.76	61.56					
49	49	23.27	35.28	49.55	76.58	44.29	43.54	89.34	25.53	89.34	80.33	60.06	18.02					
50	50	21.02	33.03	93.09	37.54	72.82	81.83	38.29	109.61	28.53	33.03	12.01	40.54					
Mean/slides		48.00	56.07	48.15	42.64	64.53	52.01	74.38	49.32	62.37	40.22	44.28	45.31					
Mean/animal																		
Meandose			50.74			53.06		52.28	62.03			43.27						

Test item: Dose.	Animal N° Slide No. BC-07- Code BC-07-14 File No. BC-07-14	CATECHOL 400 mg/kg/day (x2)			Organ	DUODENUM			1 <sup>st</sup> treatment 2 <sup>nd</sup> treatment			25/09/2007 26/09/2007				
		6518				6517			6520			6519				
		239 A H1	239 B H2	239 C H3		240 A M1	240 B M2	240 C M3	241 A S1	241 B S2	241 C S3	242 A N1	242 B N2	242 C N3		
		H1.xls	H2.xls	H3.xls		M1.xls	M2.xls	M3.xls	S1.xls	S2.xls	S3.xls	N1.xls	N2.xls	N3.xls		
No. of cell		tail length				tail length				tail length				tail length		
1		17.27	68.32	29.28	29.28	29.28	75.82	63.81	97.60	44.29	100.60	99.10	21.77	18.02		
2		122.37	70.57	27.03	111.11	111.11	70.57	93.09	16.52	57.81	12.76	137.38	63.81	62.31		
3		93.84	28.53	74.32	99.10	99.10	47.30	62.31	60.06	12.76	57.06	39.04	58.56	93.84		
4		96.85	107.36	19.52	72.07	72.07	92.34	24.77	53.30	75.07	41.29	84.08	24.02	31.53		
5		25.53	85.58	26.28	65.31	65.31	70.57	55.55	103.60	67.57	72.07	154.65	74.32	76.58		
6		54.80	99.85	83.33	57.81	57.81	109.61	58.56	126.12	136.63	8.26	64.56	66.06	28.53		
7		80.33	28.53	57.06	78.83	78.83	30.03	96.09	27.78	18.77	14.26	170.42	18.02	77.33		
8		14.26	102.85	16.52	58.56	58.56	45.04	90.09	35.28	17.27	103.60	107.36	37.54	14.26		
9		103.60	25.53	24.02	39.04	39.04	31.53	117.87	114.86	100.60	26.28	38.29	43.54	41.29		
10		89.34	132.13	111.86	84.83	84.83	98.35	24.02	97.60	169.67	70.57	49.55	36.04	57.81		
11		10.51	18.77	13.51	15.01	15.01	106.60	60.06	18.77	103.60	79.58	91.59	65.31	28.53		
12		50.30	12.76	12.76	11.26	11.26	108.86	27.78	55.55	87.84	21.77	132.13	92.34	36.31		
13		12.01	15.01	26.28	76.58	76.58	15.01	53.30	44.29	12.01	23.27	69.82	55.55	66.82		
14		40.54	53.30	11.26	93.09	93.09	87.84	75.07	40.54	36.04	12.76	97.60	18.77	66.06		
15		20.27	95.34	32.28	31.53	31.53	33.03	113.36	42.79	25.53	12.01	27.03	54.80	39.04		
16		37.54	24.02	67.57	42.04	42.04	82.58	47.30	38.29	114.11	80.33	25.53	74.32	48.05		
17		69.07	101.35	57.06	14.26	14.26	40.54	118.82	37.54	12.76	21.02	136.63	76.58	36.04		
18		29.28	127.63	83.33	56.31	56.31	87.09	30.03	63.06	103.60	12.01	120.87	60.81	22.52		
19		32.28	33.03	72.07	78.83	78.83	108.86	68.32	60.06	93.09	39.79	60.06	61.56	47.30		
20		50.30	13.51	51.05	33.03	33.03	33.03	30.03	110.36	27.78	65.31	77.33	138.89	30.03		
21		12.76	124.62	11.26	73.57	73.57	77.33	73.57	30.03	64.08	11.26	23.27	69.07	43.54		
22		105.10	25.53	39.79	73.57	73.57	18.02	26.28	12.76	52.55	123.87	39.79	47.30	37.54		
23		24.77	102.85	24.77	31.53	31.53	12.01	84.08	15.01	87.09	33.78	33.03	45.79	63.81		
24		75.07	36.79	26.28	59.31	59.31	33.78	80.33	27.78	18.02	12.76	127.63	35.28	22.52		
25		75.07	19.52	18.02	21.02	21.02	139.64	93.84	44.29	33.03	70.57	53.30	69.07	78.83		
26		9.01	63.06	83.33	39.04	39.04	105.85	86.33	26.28	29.28	44.29	61.56	73.57	64.56		
27		34.53	21.02	16.52	16.52	16.52	12.01	14.26	12.76	20.27	15.01	33.78	78.83	18.77		
28		63.06	12.76	63.06	32.28	32.28	92.34	26.28	91.59	30.78	18.02	108.86	44.29	74.32		
29		80.33	11.26	17.27	33.03	33.03	59.31	49.55	25.53	29.28	20.27	113.36	46.55	38.29		
30		37.54	89.34	60.81	30.78	30.78	66.06	76.58	18.02	59.31	33.78	31.53	27.03	50.30		
31		81.08	26.28	47.30	81.63	81.63	104.35	30.03	162.16	44.29	12.76	101.35	18.77	72.82		
32		49.55	69.07	46.55	14.26	14.26	27.78	120.12	14.26	26.28	12.76	122.37	30.78	36.04		
33		78.08	112.61	18.02	90.09	90.09	99.85	54.80	30.78	26.28	30.78	38.29	75.07	26.28		
34		50.30	112.61	18.02	35.28	35.28	36.04	142.64	74.32	15.01	47.30	60.81	38.29	91.59		
35		62.31	56.31	34.53	40.54	40.54	108.11	86.33	14.26	65.31	166.66	83.33	47.30	77.33		
36		57.81	69.07	117.87	17.27	17.27	101.35	79.58	26.28	72.07	81.08	49.55	21.77	40.54		
37		19.52	89.34	78.08	32.28	32.28	65.31	39.04	30.78	104.35	114.11	125.37	69.82	24.77		
38		55.55	78.83	12.76	36.79	36.79	98.35	27.78	25.53	61.56	71.32	69.07	22.52	38.29		
39		93.09	63.06	79.58	18.77	18.77	109.61	37.54	12.76	102.10	94.59	17.27	39.79	14.26		
40		30.78	51.80	70.57	65.31	65.31	71.32	28.53	119.37	39.04	37.54	18.02	50.30	35.28		
41		53.30	27.03	71.32	22.52	22.52	72.82	12.01	13.51	129.88	21.77	51.05	23.27	12.01		
42		60.06	66.82	29.28	71.32	71.32	27.78	30.78	12.01	25.53	85.58	30.03	60.06	12.01		
43		34.53	102.10	84.08	37.54	37.54	88.59	70.57	90.84	33.03	101.35	57.81	129.88	12.01		
44		63.81	69.82	106.60	41.29	41.29	99.10	79.58	18.02	160.66	13.51	108.86	27.03	14.26		
45		13.51	124.62	52.55	62.31	62.31	123.87	33.03	11.26	133.63	18.77	36.79	29.28	77.33		
46		25.53	39.79	140.39	77.33	77.33	61.56	61.56	12.01	23.27	92.34	53.30	22.52	77.33		
47		26.28	43.54	38.29	16.52	16.52	71.32	66.82	30.78	83.33	30.78	83.33	15.01	84.83		
48		99.10	12.01	33.78	44.29	44.29	93.84	43.54	15.01	60.06	15.01	55.55	54.80	12.01		
49		45.04	35.28	90.09	15.01	15.01	88.59	48.05	15.77	78.83	101.35	59.31	28.53	51.80		
50		16.52	98.09	70.57	35.28	35.28	94.59	74.32	133.88	11.26	12.76	83.33	88.59	24.77		
Mean/slide		51.67	59.91	51.40	46.85	46.85	72.70	61.76	48.27	61.13	48.41	74.28	49.46	46.85		
Mean/dose			54.32				60.43		55.05	52.60		56.86				

## FSR-IPL 070402 / CATECHOL / RHODIA

Test item: Dose: Animal N°	CATECHOL 200 mg/kg/day (x2)			Organ:	DUODENUM			1 <sup>st</sup> treatment: 2 <sup>nd</sup> treatment:		25/09/2007 26/09/2007			
	6524				6521			6522		6525			
	Slide No. BC-07-14 Code BC-07-14	243 A A1.xls	243 B A2.xls		243 C A3.xls	244 A P1.xls	244 B P2.xls	244 C P3.xls	245 A L1.xls	245 B L2.xls	245 C L3.xls	246 A E1.xls	246 B E2.xls
File No. BC-07-14	tail length				tail length				tail length			tail length	
No. of cell	243 A A1.xls	243 B A2.xls	243 C A3.xls	244 A P1.xls	244 B P2.xls	244 C P3.xls	245 A L1.xls	245 B L2.xls	245 C L3.xls	246 A E1.xls	246 B E2.xls	246 C E3.xls	
1	45.04	15.77	52.55	71.32	68.32	85.58	97.60	78.83	84.83	80.33	13.51	66.82	
2	105.10	12.76	62.31	15.01	27.03	53.30	98.35	80.33	66.06	99.10	15.77	24.77	
3	72.07	58.56	35.28	130.63	30.78	60.06	113.36	66.82	66.82	51.80	18.77	72.07	
4	35.28	45.04	71.32	88.59	28.53	60.81	85.58	54.80	49.55	31.53	22.52	72.82	
5	35.28	68.32	36.79	32.28	41.29	34.53	108.86	63.06	60.06	13.51	86.33	49.55	
6	57.81	26.28	48.05	63.06	57.81	72.82	14.26	77.33	69.82	34.53	75.07	38.29	
7	110.36	18.02	24.77	11.86	13.51	21.77	87.84	85.58	60.81	17.27	58.56	57.81	
8	73.57	23.27	29.28	112.61	38.29	68.32	65.31	33.03	12.01	34.53	63.81	48.05	
9	28.53	47.30	29.28	113.36	75.82	12.76	78.08	13.51	55.55	48.05	42.04	29.28	
10	47.30	57.06	45.04	27.03	35.28	70.57	18.77	72.82	26.28	36.79	54.05	24.02	
11	28.53	20.27	45.04	116.36	102.10	60.06	105.10	34.53	74.32	17.27	29.28	17.27	
12	47.30	26.28	60.81	23.27	132.86	32.28	70.57	90.84	66.06	17.27	18.77	72.82	
13	42.79	28.53	54.80	122.37	66.82	60.81	27.78	53.30	36.04	33.03	21.02	41.29	
14	60.06	26.28	98.85	99.10	66.82	86.33	156.15	79.58	89.34	12.01	14.26	87.84	
15	39.04	21.77	14.26	55.55	21.02	19.52	107.36	33.03	21.02	29.28	33.78	66.06	
16	36.04	81.83	13.51	95.34	41.29	69.82	72.07	56.31	49.55	24.77	9.01	45.79	
17	13.51	57.81	70.57	68.32	54.05	13.51	69.07	47.30	66.06	36.04	58.56	14.26	
18	40.54	39.79	60.81	27.03	39.79	41.29	48.05	46.55	45.79	48.80	40.54	35.28	
19	29.28	45.79	20.27	45.04	23.27	57.06	105.10	90.09	46.55	41.29	81.08	57.06	
20	51.05	34.53	48.80	74.32	57.06	13.51	102.10	72.07	51.80	51.05	12.76	77.33	
21	72.82	93.84	24.77	24.02	15.01	56.31	120.87	58.56	36.04	22.52	29.28	18.02	
22	45.79	24.77	11.26	67.57	13.51	93.09	65.31	58.56	27.03	45.04	18.02	39.79	
23	66.82	28.53	49.55	27.03	34.53	11.26	123.12	58.56	36.79	47.30	35.28	20.27	
24	33.78	40.54	123.12	72.82	40.54	66.82	80.33	53.30	34.53	19.52	60.06	57.81	
25	72.82	42.79	11.26	41.29	27.03	44.29	25.53	45.79	48.05	15.01	53.30	89.34	
26	56.31	81.83	32.28	93.84	55.55	29.28	143.39	57.06	66.06	54.80	63.81	42.04	
27	106.60	15.01	115.61	78.83	12.01	72.76	93.09	20.27	72.07	67.57	21.77	27.78	
28	33.78	12.76	36.04	99.10	69.82	57.81	44.29	51.05	81.08	51.05	38.29	52.55	
29	48.80	57.06	48.05	118.62	89.34	21.02	69.07	55.55	62.31	34.53	97.60	24.02	
30	60.81	38.29	45.04	112.61	65.31	47.30	54.80	45.04	54.80	25.53	33.78	80.33	
31	12.76	15.01	84.83	47.30	25.53	57.81	50.30	36.79	62.31	30.03	73.57	57.06	
32	36.04	12.76	57.81	24.77	45.79	61.56	64.56	63.06	60.81	42.79	77.33	64.56	
33	55.55	18.02	68.32	107.36	43.54	78.83	83.33	39.04	87.09	42.04	39.04	71.32	
34	105.10	21.77	18.02	28.53	18.02	30.78	39.79	48.05	66.06	45.79	30.78	64.56	
35	111.11	32.28	37.54	72.07	17.27	33.78	68.32	48.05	59.31	40.54	58.56	27.03	
36	107.36	27.78	35.28	88.59	50.30	54.80	96.09	53.30	69.07	31.53	37.54	84.83	
37	54.05	28.53	100.60	69.82	25.53	34.53	96.09	70.57	86.33	45.79	45.79	54.80	
38	36.79	57.81	67.57	39.04	29.28	14.26	75.82	126.87	69.82	9.76	41.29	66.06	
39	105.85	67.57	36.04	103.60	77.33	30.78	101.35	52.55	26.28	111.11	60.06	72.82	
40	90.09	21.02	61.56	45.04	45.04	33.03	21.77	66.06	70.57	71.32	55.55	75.82	
41	101.35	48.80	14.26	26.28	65.31	48.80	94.59	67.57	59.31	66.06	34.53	60.81	
42	92.34	27.78	16.52	51.05	60.06	50.30	108.11	36.04	54.80	108.86	24.02	66.82	
43	128.38	52.55	42.79	32.28	87.09	56.31	118.86	48.80	34.53	145.64	69.82	45.04	
44	107.36	55.55	44.29	66.82	30.03	35.28	111.86	48.80	28.53	15.77	57.06	48.05	
45	117.12	21.02	43.54	49.55	65.31	44.29	97.60	83.33	67.57	129.13	26.28	64.56	
46	92.34	18.77	12.76	56.31	29.28	35.28	60.06	67.57	61.56	87.09	30.78	75.82	
47	90.09	77.33	34.53	33.78	28.53	45.79	60.06	21.77	44.29	97.60	52.55	54.05	
48	88.59	28.53	22.52	19.52	27.03	50.30	22.52	86.33	56.31	74.32	113.36	72.82	
49	115.61	54.05	32.28	73.57	39.79	12.01	128.38	87.09	44.29	29.28	44.29	53.30	
50	39.79	15.01	22.52	72.07	57.81	60.06	16.52	48.05	95.34	36.79	72.82	79.58	
Mean/slide	66.62	38.02	44.98	66.71	46.25	46.07	78.66	59.43	56.08	48.05	45.31	54.20	
Mean/animal													
Meandose													

FSR-IPL 070402 / CATECHOL / RHODIA

Test item Dose:	CATECHOL 100 mg/kg/day (x2)			Organ.	DUODENUM			1 <sup>st</sup> treatment: 2 <sup>nd</sup> treatment:			25/09/2007 26/09/2007		
	65/7				65/29			65/26			65/30		
	247 A	247 B	247 C		248 A	248 B	248 C	249 A	249 B	249 C	250 A	250 B	250 C
Animal N° Slide No. BC-07- Code BC-07-14 File No. BC-07-14	G1	G2	G3	I1	I2	I3	R1	R2	R3	B1	B2	B3	
No. of cell	G1.xls	G2.xls	G3.xls	I1.xls	I2.xls	I3.xls	R1.xls	R2.xls	R3.xls	B1.xls	B2.xls	B3.xls	
No. of cell	Tail length												
	98.35	126.12	41.29	91.59	39.04	56.31	112.61	71.32	83.33	72.82	63.81	60.06	
	97.60	72.82	47.30	119.37	136.63	47.30	121.62	14.26	69.07	132.88	69.07	70.57	
	122.37	37.54	68.58	131.38	80.33	61.56	37.54	48.80	26.28	29.28	59.31	54.05	
	99.85	48.80	76.32	35.28	75.07	33.03	87.84	42.04	48.05	53.30	63.06	57.06	
	117.12	36.79	51.05	115.61	102.10	61.56	102.85	19.52	59.31	78.83	14.26	11.26	
	135.13	45.79	69.07	66.82	31.53	25.53	90.84	84.83	16.52	118.62	83.33	61.56	
	75.92	89.34	83.33	104.35	74.32	75.82	60.06	66.82	42.04	52.55	75.07	90.09	
	115.61	71.32	75.82	18.02	108.86	27.78	141.89	66.06	124.62	104.35	74.32	57.06	
	107.36	25.53	55.55	105.85	58.56	101.35	119.37	49.55	60.81	24.77	54.05	66.06	
	114.11	65.31	48.80	70.57	59.31	31.53	123.12	41.29	40.54	96.09	81.08	75.82	
	108.86	78.83	29.28	64.56	48.05	20.27	69.82	35.28	56.31	51.05	13.51	73.57	
	108.11	111.86	42.79	90.84	48.05	58.56	105.85	56.31	56.31	96.09	57.06	75.82	
	153.15	76.58	45.04	96.35	78.08	36.04	157.65	157.65	63.06	15.77	15.01	55.55	73.57
	153.15	53.30	24.02	125.37	25.53	51.05	90.09	90.09	66.06	20.27	88.59	58.56	32.28
	117.12	45.79	87.09	113.36	84.83	39.04	111.11	111.11	42.04	14.26	50.30	35.28	74.32
	102.10	57.81	53.30	96.09	67.57	14.26	118.62	118.62	19.52	49.55	39.04	31.53	69.82
	54.05	57.81	20.27	99.85	57.81	65.31	80.33	80.33	63.06	46.55	66.06	47.30	52.55
	108.86	60.81	39.04	39.04	113.36	36.04	84.08	84.08	75.82	24.02	26.28	57.81	68.32
	47.30	96.85	15.01	28.53	68.32	87.09	87.84	87.84	15.01	45.79	36.79	42.79	11.26
	88.59	81.83	76.58	86.59	72.82	63.06	136.63	136.63	60.81	33.78	72.82	25.53	78.08
	116.36	88.59	54.80	176.42	59.31	42.04	56.31	56.31	106.60	33.78	27.78	56.31	28.53
	102.10	78.08	47.30	112.61	40.54	80.33	99.85	99.85	73.57	43.54	14.26	38.29	78.08
	100.60	31.53	93.09	47.30	129.13	69.07	87.84	87.84	17.27	41.29	54.05	57.81	65.31
	69.07	99.85	77.33	178.68	27.78	59.31	129.88	129.88	67.57	46.55	76.58	81.08	60.06
	81.08	18.02	58.56	84.83	86.33	70.57	14.26	14.26	78.83	48.80	21.02	57.81	43.54
	116.36	90.09	68.82	104.35	33.03	69.07	78.08	78.08	78.08	25.53	87.84	79.58	93.09
	55.55	114.86	63.06	63.81	12.76	70.57	45.04	45.04	75.82	13.51	15.77	67.57	69.82
	80.33	53.30	21.78	103.60	15.77	24.77	58.56	137.38	76.06	58.56	33.03	58.56	14.26
	83.33	90.84	45.79	44.29	13.51	36.79	57.06	141.89	56.31	34.53	15.77	64.56	54.80
	91.59	27.03	33.78	102.10	36.79	69.82	32.28	137.38	85.58	33.03	46.55	53.30	63.81
	56.31	30.78	43.54	103.60	69.82	25.53	63.81	32.28	63.81	19.52	27.03	45.04	36.79
	21.02	79.58	36.79	80.33	47.30	74.32	59.31	59.31	72.82	43.54	27.78	22.52	62.31
	87.09	87.84	76.58	104.35	67.57	90.84	54.05	54.05	79.58	11.26	41.29	19.52	69.07
	49.55	24.77	57.06	63.06	23.27	67.57	64.56	64.56	54.80	15.01	20.27	14.26	57.81
	30.78	54.05	57.06	84.83	27.03	67.57	15.77	60.81	34.53	63.06	39.79	36.04	66.82
	135.13	73.57	64.56	27.78	27.78	69.07	42.04	31.53	75.07	39.79	12.01	12.76	36.04
	95.34	88.59	57.81	122.37	47.30	105.10	18.77	18.77	73.57	30.78	96.85	43.54	33.78
	132.13	21.78	15.01	26.28	12.76	69.82	68.32	30.78	78.83	15.77	37.54	44.29	90.09
	143.39	72.82	48.05	99.10	32.28	32.28	68.32	103.60	12.01	42.04	23.27	22.52	45.79
	33.03	70.57	45.04	114.86	83.33	60.81	60.81	109.61	77.33	33.03	64.56	20.27	62.31
	19.52	98.35	12.76	77.33	118.62	51.80	51.80	32.28	66.82	27.03	30.03	30.03	28.53
	134.38	61.56	67.57	155.40	78.83	23.27	43.54	43.54	20.27	33.78	102.10	15.77	15.77
	142.64	39.04	44.29	102.10	125.37	90.09	90.09	47.30	39.79	24.02	97.60	30.03	64.56
	30.03	72.07	54.05	95.34	70.57	45.79	65.31	65.31	21.77	24.77	119.37	30.78	17.27
	86.33	41.29	52.55	102.85	57.06	68.32	49.55	49.55	59.31	32.28	118.62	19.52	79.58
	87.84	61.56	28.53	108.11	78.83	63.81	63.81	42.04	43.54	14.26	116.36	94.59	62.31
	10.51	42.04	47.30	60.81	23.27	86.33	86.33	36.04	60.81	19.52	112.61	84.83	69.07
	134.38	94.59	49.55	86.33	55.55	55.55	64.56	87.84	18.77	30.78	45.04	87.09	48.05
	69.82	55.55	21.02	103.60	33.03	33.03	76.58	34.53	22.52	33.78	41.29	39.79	54.80
105.85	112.61	40.54	51.80	83.33	83.33	69.07	114.11	36.79	33.03	122.37	61.56	66.82	
92.52	66.44	50.75	89.83	61.79	61.79	57.07	81.02	54.64	37.99	59.88	49.04	57.04	
Mean/slide													
Mean/animal													
Mean/dose		69.90			69.56		63.17	57.88		55.32			

Test item:		Dimethylhydrazine 20 mg/kg/day (x1)				Organ:				DUODENUM			
Dose		6535				6537				6538			
Animal No.	Animal ID	236 A	236 B	236 C		237 A	237 B	237 C		238 A	238 B	238 C	
Slide No. BC-07-		J1	J2	J3		F1	F2	F3		C1	C2	C3	
Code BC-07-14		J1.xls	J2.xls	J3.xls		F1.xls	F2.xls	F3.xls		C1.xls	C2.xls	C3.xls	
File No. BC-07-14		J1.xls	J2.xls	J3.xls		F1.xls	F2.xls	F3.xls		C1.xls	C2.xls	C3.xls	
No. of cell		Tail length				Tail length				Tail length			
1		96.09	87.09	64.56		86.33	33.03	101.35		27.78	99.10	117.12	
2		91.59	88.59	48.05		96.09	44.29	99.34		105.85	44.29	69.82	
3		56.31	109.61	94.59		87.09	24.77	82.58		107.36	85.58	20.27	
4		69.82	78.83	54.05		77.33	79.58	52.55		82.58	42.04	37.54	
5		87.09	96.85	86.33		92.34	87.84	110.36		101.35	129.13	66.82	
6		57.81	75.82	84.83		44.29	43.54	140.39		80.33	70.57	56.31	
7		78.83	57.81	60.81		79.58	19.52	78.83		99.10	65.31	94.59	
8		105.85	35.28	91.59		90.09	99.10	72.07		106.60	72.07	18.02	
9		57.06	102.85	96.09		81.08	95.34	81.08		99.85	115.61	71.32	
10		81.83	121.62	45.79		63.06	93.84	67.57		74.32	27.78	81.08	
11		60.81	96.09	49.55		57.81	99.85	92.34		71.32	22.52	76.58	
12		60.06	89.34	99.10		99.85	94.59	79.58		56.31	60.06	89.34	
13		70.57	58.56	117.87		86.33	74.32	67.57		89.34	109.61	42.79	
14		75.82	78.83	92.34		99.85	93.09	28.53		42.79	95.34	48.80	
15		97.60	96.85	63.06		94.59	68.32	72.07		69.07	105.85	65.31	
16		95.34	53.30	98.35		90.84	92.34	105.10		59.31	78.08	71.32	
17		106.60	45.79	71.32		118.62	72.07	109.61		57.81	90.09	100.60	
18		54.05	43.54	68.32		81.08	48.05	39.79		77.33	69.82	68.32	
19		100.60	39.04	73.57		69.82	83.33	41.29		57.81	51.05	98.35	
20		90.84	75.82	75.07		104.35	66.06	34.53		57.81	45.04	87.09	
21		106.60	76.56	129.13		96.09	72.82	91.59		54.05	43.54	114.11	
22		57.06	51.05	85.58		79.58	78.08	69.82		74.32	63.06	50.30	
23		70.57	78.83	43.54		82.58	138.14	120.12		56.31	45.04	99.85	
24		63.81	111.86	54.80		65.31	60.81	64.56		65.31	45.04	99.85	
25		72.07	84.83	61.56		113.36	173.42	146.39		60.81	82.58	80.33	
26		36.04	106.60	97.60		99.85	36.79	113.36		61.56	41.29	77.33	
27		98.35	75.82	105.10		93.09	48.05	96.09		91.59	53.30	83.33	
28		69.82	105.85	77.33		105.85	65.31	24.02		72.07	50.30	129.13	
29		69.07	66.82	58.56		95.34	83.33	149.40		93.09	71.32	84.08	
30		63.06	111.11	64.56		25.53	33.78	108.86		63.06	47.30	87.84	
31		56.31	102.10	42.79		21.77	36.79	93.84		90.84	135.13	86.33	
32		28.53	124.62	60.81		69.07	61.56	81.08		55.55	60.06	89.34	
33		78.08	143.39	113.36		78.08	62.31	80.33		99.10	89.34	84.08	
34		63.06	59.31	94.59		61.56	42.04	83.33		13.51	52.55	92.34	
35		87.09	107.36	75.82		87.09	69.82	135.88		68.32	33.03	117.12	
36		102.85	84.08	62.31		40.54	94.59	45.79		81.83	107.36	126.87	
37		49.55	63.06	81.08		69.07	107.36	63.06		70.57	54.05	119.37	
38		107.36	65.31	51.05		94.59	102.85	78.83		77.33	81.08	52.55	
39		46.55	96.85	58.56		86.33	56.31	64.56		89.34	53.30	51.05	
40		84.83	89.34	66.06		45.79	56.31	77.33		93.84	40.54	98.35	
41		33.03	77.33	39.04		70.57	66.82	93.84		71.32	81.83	102.10	
42		69.07	146.39	65.31		94.59	152.40	98.85		123.12	72.82	21.02	
43		67.57	75.82	66.82		104.35	77.33	83.33		81.83	65.31	69.82	
44		53.30	77.33	117.12		117.12	113.36	43.54		75.82	99.10	92.34	
45		140.39	118.62	67.57		57.06	78.83	138.89		55.55	85.58	41.29	
46		44.29	42.04	63.81		79.58	93.09	99.10		94.59	135.13	96.85	
47		62.31	47.30	61.56		87.09	121.62	80.33		55.55	75.82	75.82	
48		19.52	35.28	80.33		89.34	102.85	64.56		60.81	72.07	45.04	
49		35.28	91.59	93.09		111.11	104.35	84.08		53.30	21.77	41.29	
50		41.29	94.59	76.58		66.06	102.10	83.33		112.61	93.84	74.32	
Mean/slide		71.43	82.91	74.22		81.76	78.12	84.49		74.73	71.27	77.48	
Mean/animal													
Mean/dose			76.18				81.45				74.49		

## Appendix No. 12: Individual values for Percentage of DNA / DUODENUM

Test item:	Dose	Distilled water 0 mg/kg/day (x2)	Organ	DUODENUM		1 <sup>st</sup> treatment:		25/09/2007	
				6512		6514		6511	
Slide No. BC-07-14	232 A	232 B	232 C	233 A	233 B	233 C	234 A	234 B	235 C
File No. BC-07-14	Q1.xls	Q2.xls	Q3.xls	K1.xls	K2.xls	K3.xls	D1.xls	D2.xls	O3.xls
No. of cell	% DNA in tail			% DNA in tail			% DNA in tail		
1	5.76	31.36	3.13	37.95	2.63	56.58	85.18	41.40	0.39
2	30.94	39.91	4.88	8.72	1.29	6.42	50.82	83.60	10.93
3	20.20	0.42	0.03	1.08	14.50	25.04	82.59	40.41	0.72
4	69.02	1.43	13.02	17.19	70.45	0.81	73.84	54.99	38.66
5	51.69	1.81	17.72	22.79	1.22	43.59	53.85	20.31	26.91
6	65.76	0.56	25.75	7.17	21.73	39.24	39.24	45.80	10.23
7	71.25	6.47	0.24	25.73	4.22	18.59	85.34	0.00	61.32
8	4.44	1.02	4.97	3.82	44.37	23.52	85.75	1.91	0.04
9	1.18	30.22	0.29	19.84	40.96	0.47	22.15	41.15	13.93
10	0.35	19.34	0.27	61.75	9.67	17.66	12.81	12.67	26.13
11	54.06	12.46	23.61	1.49	2.17	28.41	4.12	9.67	75.53
12	20.22	0.19	1.08	0.31	19.68	0.18	63.09	44.39	16.51
13	9.71	0.87	1.03	28.28	4.57	12.96	53.36	0.00	0.33
14	6.78	0.00	7.84	75.49	49.68	0.00	7.05	2.58	6.97
15	0.02	6.95	33.01	36.48	55.60	0.04	64.48	0.03	69.25
16	0.44	17.01	51.28	0.01	41.27	42.41	69.99	49.64	0.24
17	0.00	7.94	3.26	0.29	40.31	3.11	0.00	5.97	0.99
18	0.11	61.49	31.95	0.11	3.38	1.48	52.82	27.13	60.79
19	19.52	9.37	0.50	16.51	0.00	9.57	4.86	8.98	45.31
20	0.00	53.68	46.68	0.00	18.79	6.94	88.33	19.84	83.26
21	0.00	54.32	3.08	13.57	5.53	24.68	1.77	39.50	62.45
22	72.89	10.56	14.57	2.19	12.22	8.98	66.64	1.72	33.63
23	1.43	1.08	36.46	0.00	13.48	23.19	17.78	0.07	0.43
24	77.69	2.33	22.23	44.73	19.19	27.17	89.43	7.69	16.07
25	19.50	6.03	41.43	0.00	9.14	34.57	81.36	8.97	20.66
26	41.05	2.36	0.14	0.15	35.98	1.07	81.03	4.43	1.53
27	0.64	62.78	14.33	0.43	11.89	46.88	83.91	3.98	44.52
28	0.97	9.35	56.07	30.55	14.54	2.90	1.29	37.55	16.50
29	2.78	8.45	20.25	40.01	7.39	24.06	72.75	0.09	43.44
30	10.81	3.88	31.97	0.27	0.34	22.08	3.73	7.02	48.52
31	12.09	25.52	2.37	0.00	20.82	3.82	68.10	9.99	28.62
32	12.60	71.48	4.85	3.86	72.68	56.72	6.13	13.14	13.68
33	59.17	28.14	0.09	14.39	17.73	54.95	76.52	35.93	40.22
34	67.03	9.34	0.00	55.07	29.35	7.34	56.58	8.96	29.58
35	9.74	0.07	26.44	0.33	30.75	0.03	49.85	31.14	0.00
36	0.01	5.75	0.04	8.53	4.23	0.12	85.29	2.95	73.66
37	1.25	5.60	47.09	0.01	52.44	1.72	0.17	0.88	2.46
38	41.97	11.24	1.91	0.74	13.23	1.49	21.97	46.95	5.73
39	2.94	22.07	75.90	1.93	40.32	76.89	79.18	7.62	6.43
40	0.01	0.37	6.23	5.20	2.83	9.95	36.63	0.47	0.51
41	44.98	16.35	43.66	68.81	43.07	0.02	18.70	4.52	50.79
42	66.83	42.83	59.01	1.56	0.00	4.22	16.37	81.71	61.55
43	57.55	0.00	14.87	2.04	28.73	5.32	33.23	46.30	43.16
44	14.86	0.45	8.90	63.60	49.22	0.00	33.99	59.29	29.41
45	32.35	0.00	2.35	1.30	15.16	25.58	18.08	24.25	35.65
46	3.86	50.63	45.90	0.01	0.36	18.59	40.89	0.00	0.00
47	0.25	15.98	0.56	0.53	47.45	0.01	0.00	0.00	16.82
48	2.38	5.81	20.71	29.45	57.87	59.60	16.26	41.86	3.21
49	0.10	8.46	13.11	27.49	4.90	29.36	18.01	0.02	4.26
50	0.05	4.18	44.50	2.37	21.40	10.41	5.32	57.89	31.63
Mean/side	21.94	15.76	18.59	15.68	22.14	17.96	43.61	21.94	12.21
Mean/animal	21.94	15.76	18.59	15.68	22.14	17.96	43.61	21.94	12.21
Mean/dose	21.94	15.76	18.59	15.68	22.14	17.96	43.61	21.94	12.21

Dose	6518				6517				6520				6519			
	239 A H1.xls	239 B H2	239 C H3	% DNA in tail	240 A M1.xls	240 B M2	240 C M3	% DNA in tail	241 A S1.xls	241 B S2	241 C S3	% DNA in tail	242 A N1.xls	242 B N2	242 C N3	
Slide No. BC-07-Code BC-07-14																
File No. BC-07-14																
No. of cell																
1	0.15	61.09	1.68		0.66	23.20	7.92		60.89	1.80	54.56		22.87	1.04	8.36	
2	54.46	14.60	1.97		8.27	29.54	58.81		2.33	5.69	0.10		65.66	35.04	35.58	
3	77.86	0.40	21.29		57.79	13.65	8.96		28.67	0.09	15.75		0.26	34.92	45.24	
4	44.29	84.23	0.00		46.22	12.60	3.23		4.85	32.52	0.39		12.97	2.53	3.09	
5	0.05	33.84	0.16		32.34	11.47	3.30		40.29	9.96	29.01		77.76	79.61	76.01	
6	29.43	64.31	38.06		3.69	18.92	4.25		46.74	50.93	0.00		48.79	61.52	3.25	
7	5.35	2.25	6.63		68.30	74.19			1.33	0.08	0.02		82.62	1.07	78.37	
8	0.00	76.73	0.04		14.86	27.30	32.05		1.56	0.40	67.75		58.29	3.51	0.28	
9	63.85	0.62	5.92		8.54	0.65	52.08		51.10	25.94	3.99		1.44	3.01	23.22	
10	50.66	60.89			48.42	24.37	0.07		38.81	83.94	14.94		0.90	18.49	33.77	
11	0.00	0.01	0.00		1.12	23.58	4.58		0.11	30.21	66.28		23.43	49.31	1.96	
12	4.68	0.00	0.00		5.92	42.93	11.05		11.50	13.53	0.19		48.60	48.55	20.25	
13	0.00	0.00	3.17		52.11	7.20	16.18		6.68	0.06	0.00		9.80	25.34	35.34	
14	4.77	26.43	0.00		82.96	40.96	7.37		0.57	9.68	0.00		59.57	0.00	71.06	
15	0.01	67.46	5.45		1.78	6.50	34.74		1.61	0.05	0.00		1.37	0.10	8.73	
16	13.05	0.17	44.50		8.27	37.51	15.64		8.38	7.47	25.54		0.17	32.57	7.73	
17	6.38	56.23	19.76		0.46	19.16	55.69		2.57	0.05	0.10		76.16	34.62	11.00	
18	1.02	76.05	15.82		33.18	46.88	5.90		10.40	70.05	0.12		67.26	2.10	3.90	
19	2.19	3.86	28.00		83.09	83.44	15.57		10.40	75.45	0.32		37.06	50.62	12.66	
20	17.59	0.00	13.48		3.04	11.30	0.14		76.41	0.00	0.06		5.10	60.42	1.72	
21	0.00	56.19	2.83		14.80	39.82	9.99		0.11	28.30	0.13		0.90	34.72	14.24	
22	73.87	0.02	2.52		64.63	3.40	1.85		0.00	10.69	92.84		4.27	9.96	5.78	
23	0.06	73.94	0.41		5.57	0.60	49.22		0.01	38.58	1.09		14.35	16.56	21.48	
24	61.49	0.18	0.16		39.42	5.31	20.82		1.43	0.00	1.15		44.91	14.61	0.42	
25	19.51	1.11	0.11		3.75	68.08	30.23		4.41	20.54	61.44		17.96	37.72	84.75	
26	2.39	9.61	34.76		49.59	16.66	22.50		0.50	8.11	41.70		5.54	41.73	57.57	
27	7.50	0.01	0.08		0.00	0.00	4.81		0.29	0.00	0.73		7.56	56.56	0.00	
28	28.03	0.27	21.25		2.33	32.68	0.05		59.42	0.01	15.87		56.78	12.07	41.94	
29	56.27	1.51	0.03		2.11	27.04	10.44		0.04	0.01	18.44		57.18	11.15	2.99	
30	2.36	38.66	28.76		1.16	10.40	12.48		0.04	31.96	0.08		0.54	0.09	4.77	
31	55.73	1.28	9.18		18.81	34.94	0.72		55.68	11.92	0.00		32.44	0.90	82.28	
32	2.21	38.91	10.30		0.05	4.01	80.78		0.18	0.14	0.00		37.30	0.11	6.34	
33	44.76	0.00	45.94		4.19	37.38	4.33		1.46	0.26	5.40		2.11	61.48	2.31	
34	6.97	85.59	2.17		6.63	2.43	71.06		31.93	0.22	16.25		15.46	2.91	82.63	
35	19.00	4.40	8.83		8.44	32.27	33.09		0.02	34.73	95.23		37.83	4.57	81.37	
36	2.24	3.16	48.90		14.87	47.73	66.88		0.04	32.94	44.17		4.46	0.17	14.24	
37	2.43	50.96	47.63		7.96	33.78	4.18		3.58	33.93	83.74		62.57	17.85	0.97	
38	2.73	24.98	0.00		35.97	34.41	2.29		2.67	22.97	42.55		14.91	0.03	2.02	
39	75.45	2.42	70.13		0.58	59.99	16.49		0.00	3.84	39.96		0.09	5.81	0.16	
40	0.08	1.88	38.60		15.96	28.46	1.72		48.93	3.03	11.77		6.89	1.16	11.28	
41	4.36	0.90	21.53		6.45	24.55	0.00		0.00	75.98	0.26		32.19	0.68	2.82	
42	4.75	2.86	0.23		8.84	16.52	16.52		0.00	0.16	49.66		18.13	10.79	2.12	
43	0.38	62.93	69.44		2.00	69.95	65.56		36.98	0.14	61.26		46.35	1.26	82.28	
44	24.52	17.74	72.22		5.20	60.13	16.32		0.43	61.96	0.03		56.52	1.48	0.60	
45	0.01	53.73	0.04		18.27	71.39	0.93		0.00	63.95	0.00		2.21	2.58	0.13	
46	1.03	4.04	76.58		48.10	7.78	12.55		0.00	0.64	61.35		8.45	1.16	81.97	
47	0.53	0.84	7.38		0.72	8.14	35.44		0.02	32.12	0.66		28.72	0.22	62.13	
48	92.58	0.00	1.37		14.89	36.49	1.68		0.01	21.18	1.64		33.44	10.08	1.61	
49	10.98	3.97	35.88		0.03	55.33	4.38		0.05	40.48	72.98		14.02	0.76	9.05	
50	0.01	45.74	9.12		37.89	48.71	15.09		67.12	0.00	0.83		29.45	82.70	0.06	
Mean/Slide	20.16	24.79	18.72		19.85	27.95	20.49		14.41	20.10	22.19		27.83	19.68	24.84	
Mean/animal		21.23				22.76				18.90				24.12		

Test item: Dose	Animal N°	CATECHOL 200 mg/kg/day (x2)			Organ	DUODENUM			1 <sup>st</sup> treatment 25/09/2007		2 <sup>nd</sup> treatment 26/09/2007		6525		
		243 A	243 B	243 C		244 A	244 B	244 C	245 A	245 B	245 C	246 A	246 B	246 C	
		A1	A2	A3	P1	P2	P3	L1	L2	L3	E1	E2	E3		
File No. BC-07-14		A1.xls	A2.xls	A3.xls	P1.xls	P2.xls	P3.xls	L1.xls	L2.xls	L3.xls	E1.xls	E2.xls	E3.xls		
No. of cell		% DNA in tail			% DNA in tail			% DNA in tail			% DNA in tail				
1		2.70	1.23	19.53	1.94	24.11	80.79	73.58	67.08	70.85	56.50	0.00	62.18		
2		47.13	0.28	71.22	0.01	0.15	24.27	68.38	38.62	55.76	91.21	1.38	10.03		
3		20.49	17.13	6.99	79.92	0.32	69.28	69.00	31.86	75.74	21.55	0.65	69.27		
4		1.61	11.78	30.79	57.50	0.80	60.17	24.74	3.49	13.32	19.84	1.36	59.86		
5		0.00	15.38	3.91	14.20	9.51	2.93	82.66	19.77	25.66	6.44	74.98	40.74		
6		30.00	0.99	42.63	25.01	99.19	59.91	0.05	30.39	70.91	14.89	64.81	43.03		
7		74.93	0.37	0.05	31.88	0.95	0.03	36.83	39.23	36.15	1.50	29.84	45.66		
8		18.99	0.24	26.35	68.60	10.23	39.48	57.97	3.00	36.58	38.92	45.60	8.00		
9		0.60	16.59	3.67	56.41	74.18	0.00	50.01	0.05	36.58	57.09	10.16	3.66		
10		26.11	10.64	39.26	1.17	6.04	63.43	1.77	55.50	1.32	52.00	12.18	10.67		
11		82.13	3.07	6.09	50.30	79.92	28.57	66.66	2.28	35.65	1.06	2.09	0.25		
12		12.06	0.00	68.31	0.05	97.41	2.67	2.70	44.03	32.75	2.26	5.55	70.26		
13		8.39	0.06	37.71	58.03	35.99	94.31	1.85	13.57	10.16	32.19	6.15	14.65		
14		36.61	1.40	81.93	16.70	50.69	66.09	77.62	54.26	66.01	0.03	0.01	74.81		
15		24.92	0.39	0.01	23.30	0.07	1.69	56.35	18.82	0.09	10.61	31.37	28.86		
16		3.94	35.96	0.05	48.78	7.79	57.63	70.48	27.57	99.03	0.22	0.00	10.94		
17		0.00	11.12	51.28	38.77	22.29	0.01	66.33	14.08	13.91	25.35	52.84	0.07		
18		27.87	12.81	66.95	7.92	2.06	24.17	4.75	2.53	13.24	52.53	9.11	5.01		
19		9.04	11.09	1.07	3.99	1.06	51.53	64.45	65.86	23.57	19.88	39.40	32.31		
20		4.73	2.54	7.07	19.91	62.88	2.46	52.07	21.43	23.39	36.12	0.00	49.84		
21		51.73	97.24	0.13	0.10	0.27	42.83	78.54	45.11	1.58	8.48	1.52	0.08		
22		36.90	3.53	0.00	9.07	0.00	23.25	18.13	27.43	0.09	46.54	5.52	13.14		
23		48.75	4.67	16.55	0.88	10.15	0.00	64.20	13.65	1.60	40.44	21.92	0.19		
24		0.04	11.43	79.61	26.48	32.05	41.40	31.95	7.70	3.21	0.56	46.72	36.38		
25		21.50	4.88	0.00	5.02	5.95	0.19	0.01	16.47	39.43	0.02	28.74	52.34		
26		18.05	27.92	11.76	31.48	19.92	11.74	58.97	5.26	23.32	25.26	27.37	30.37		
27		41.47	1.71	98.92	7.75	0.00	0.00	65.96	0.12	21.38	23.27	0.76	1.59		
28		2.69	0.00	6.92	15.52	35.42	50.38	98.60	12.25	70.73	26.28	0.40	17.35		
29		0.51	19.91	32.66	45.86	86.29	1.73	29.66	35.07	28.23	10.70	67.92	7.11		
30		8.25	12.70	22.91	35.74	35.34	4.06	21.32	2.10	41.20	0.25	4.93	48.24		
31		0.00	0.01	48.57	29.26	0.75	37.14	24.35	3.77	47.86	4.50	57.43	41.49		
32		6.85	0.12	58.52	0.14	7.39	36.60	9.32	30.02	37.40	36.40	60.98	45.31		
33		13.99	1.32	60.36	40.96	17.55	9.01	38.55	21.14	89.44	37.18	0.17	86.55		
34		77.38	15.12	0.02	0.39	1.53	3.40	4.13	27.01	61.04	25.44	0.07	41.86		
35		46.47	8.19	13.44	24.73	0.04	14.34	17.59	9.69	57.23	4.05	27.05	8.39		
36		49.48	1.44	8.36	49.33	26.31	40.64	18.36	14.95	45.72	6.14	18.82	59.89		
37		21.64	0.02	70.21	16.91	0.52	14.50	62.05	39.29	84.72	33.03	11.70	17.96		
38		5.34	51.77	41.39	8.99	0.51	0.83	62.71	76.62	41.11	0.00	10.52	41.60		
39		74.75	45.62	19.91	58.83	36.40	2.70	17.54	69.00	0.09	80.33	13.63	62.64		
40		24.54	8.13	72.96	11.30	2.76	10.97	72.69	35.13	75.14	26.62	12.57	78.48		
41		41.15	12.60	0.01	0.03	25.18	28.33	0.19	30.94	33.92	99.19	9.03	27.71		
42		35.18	9.28	1.29	11.47	35.20	5.34	56.94	51.31	32.05	74.57	3.58	49.78		
43		22.64	31.85	13.82	3.94	80.12	30.05	14.90	2.38	10.00	73.88	23.77	12.25		
44		76.61	41.42	13.84	20.41	5.67	7.45	42.35	8.31	13.54	14.50	8.61	30.93		
45		85.44	1.43	13.53	15.40	4.06	5.22	20.25	39.05	29.41	62.74	0.45	65.78		
46		43.01	0.07	0.00	16.75	4.28	4.43	0.00	21.95	21.34	68.59	6.52	28.19		
47		48.67	56.03	3.39	22.06	3.48	15.80	10.65	2.45	21.37	47.07	29.94	16.24		
48		28.62	0.20	0.72	7.88	1.91	17.90	2.92	68.38	50.08	66.74	65.54	24.40		
49		82.23	21.55	7.06	18.84	0.70	1.58	74.64	77.50	29.31	6.83	31.31	15.54		
50		5.26	0.32	3.65	61.38	7.43	20.61	1.72	7.14	40.80	13.18	47.84	73.57		
Mean/Slide		29.03	12.87	25.71	24.02	20.86	24.76	39.04	33.75	35.12	30.06	20.65	33.51		
Mean/animal															
Mean/dose			22.54			23.21		26.89				28.07			

## FSR-IPL 070402 / CATECHOL / RHODIA

Test item:

CATECHOL  
100 mg/kg/day (x2)

Organ:

DUODENUM

1<sup>st</sup> treatment:  
2<sup>nd</sup> treatment:25/09/2007  
26/09/2007

Animal N°	Slide No. BC-07-Code BC-07-14	File No. BC-07-14	6527			6529			6526			6530		
			247 A	247 B	247 C	248 A	248 B	248 C	249 A	249 B	249 C	250 A	250 B	250 C
No. of cell	G1.xls	G2.xls	% DNA in tail			I1.xls	I2.xls	I3.xls	R1.xls	R2.xls	R3.xls	B1.xls	B2.xls	B3.xls
			G1.xls	G2.xls	G3.xls									
1	74.15	73.15	51.60			77.07	7.06	44.01	40.61	29.04	21.21	14.37	62.87	8.19
2	76.33	52.37	36.67			88.34	9.97	9.52	36.65	0.00	46.39	14.37	22.05	45.62
3	86.29	5.07	34.68			44.71	80.96	16.90	0.53	65.48	17.71	0.98	39.38	34.58
4	9.11	27.33	34.42			5.26	59.87	8.19	16.70	13.50	17.71	2.16	52.44	8.80
5	62.39	10.72	16.33			35.92	84.84	54.66	85.43	0.22	64.40	17.17	1.95	0.00
6	86.69	7.74	55.36			13.67	1.76	0.02	43.86	93.14	1.15	64.71	84.55	16.56
7	7.67	86.45	34.14			68.70	11.08	56.80	1.03	76.24	2.86	4.20	39.75	90.97
8	79.77	38.92	71.23			1.36	60.07	7.73	52.25	41.94	7.73	76.47	53.52	17.78
9	55.76	2.03	55.15			71.82	25.88	99.31	88.39	3.12	20.34	0.05	24.86	23.97
10	81.66	13.78	44.01			12.68	27.06	5.12	12.78	5.21	1.26	19.32	25.85	56.56
11	71.86	42.21	5.30			8.89	13.46	3.84	44.36	4.53	6.18	12.97	1.98	27.02
12	82.54	67.39	24.20			19.95	50.11	12.35	73.85	23.86	15.07	76.25	5.56	33.65
13	68.65	67.93	41.29			79.43	87.12	16.17	73.85	23.72	2.98	0.01	32.68	33.59
14	79.86	10.36	14.88			87.15	0.05	45.50	31.92	35.21	0.03	18.24	17.51	0.79
15	54.25	6.03	56.69			81.87	85.37	17.04	56.59	8.87	0.10	33.44	0.07	46.67
16	54.77	29.35	54.39			23.99	23.19	0.44	47.72	1.86	40.80	2.56	17.85	21.88
17	26.04	27.86	4.49			42.41	2.21	36.73	40.50	53.75	6.71	51.34	20.25	14.80
18	39.92	48.03	14.59			1.46	73.07	0.24	29.99	37.54	0.27	0.56	32.19	35.49
19	19.13	94.25	4.11			4.69	72.96	82.55	42.36	0.02	34.01	1.82	18.47	0.00
20	43.00	61.18	53.66			25.20	44.50	61.04	49.49	66.83	13.62	28.56	0.05	30.94
21	53.55	84.03	43.66			87.11	27.50	18.09	24.02	76.23	21.11	0.28	12.37	0.01
22	86.68	81.99	22.72			83.30	60.76	54.59	53.41	31.52	14.39	0.02	6.37	37.39
23	78.94	0.35	89.27			9.01	73.77	33.45	14.88	5.78	16.41	24.91	39.18	33.57
24	40.18	74.06	86.49			75.55	2.81	18.77	74.44	22.85	33.95	64.61	46.81	1.85
25	71.86	0.47	17.22			8.74	47.04	80.93	0.00	30.27	19.46	0.13	9.73	2.24
26	86.73	93.80	60.98			78.75	4.73	23.84	3.56	59.15	15.33	29.64	46.45	16.37
27	49.82	39.07	71.36			14.24	0.00	78.03	4.06	61.82	0.59	0.26	8.56	63.77
28	17.18	15.84	0.71			73.52	0.00	0.02	51.92	1.55	29.28	7.52	16.97	0.23
29	23.46	51.97	13.75			7.94	0.00	29.28	45.94	26.82	9.58	0.44	41.17	9.75
30	61.56	0.96	3.96			83.94	20.17	28.95	64.74	62.89	10.83	42.25	19.16	22.54
31	17.55	1.76	19.54			58.93	80.22	0.23	2.80	14.12	4.00	0.38	12.62	3.40
32	5.76	18.17	1.44			47.79	19.70	53.25	23.84	3.16	18.32	4.59	4.67	26.92
33	46.07	43.64	78.31			61.89	23.21	95.47	28.83	39.10	0.94	20.43	11.40	20.06
34	17.05	0.00	14.08			44.05	0.01	32.46	46.04	4.42	0.02	0.03	0.69	40.56
35	6.26	24.90	49.45			53.41	0.47	0.14	39.65	5.39	52.77	3.49	13.68	24.79
36	63.17	55.90	54.66			2.24	35.25	1.58	19.74	52.81	11.55	0.00	0.00	5.04
37	16.72	72.34	61.12			50.79	5.72	85.86	3.40	30.26	7.75	34.37	17.02	0.22
38	73.91	0.14	0.07			0.08	0.00	62.88	1.30	55.56	0.41	0.88	13.71	49.75
39	70.42	54.21	22.16			54.90	5.63	70.77	50.62	0.00	24.55	0.24	0.05	4.99
40	16.59	84.16	23.74			61.00	44.04	58.95	59.24	63.29	12.42	10.00	0.01	19.43
41	0.66	86.08	0.00			24.72	71.30	26.41	6.06	42.79	14.53	0.46	0.15	5.04
42	69.79	32.82	83.04			70.72	37.06	0.16	28.59	0.00	21.30	53.63	0.00	1.39
43	81.46	14.19	21.88			64.52	70.11	81.32	22.58	0.22	11.08	51.52	3.67	28.85
44	22.14	20.82	27.06			33.36	36.67	8.90	47.01	0.78	11.08	38.50	0.00	0.02
45	11.83	0.80	6.43			28.86	10.24	77.44	41.48	23.86	9.84	34.66	0.18	56.87
46	38.22	36.93	0.90			72.14	35.90	61.59	20.63	2.56	0.93	13.28	22.98	21.04
47	0.11	22.35	52.20			16.79	1.16	89.77	0.30	38.69	5.64	44.74	6.71	30.08
48	85.14	15.76	23.02			22.11	27.24	36.48	29.83	4.01	4.01	8.12	60.32	13.23
49	14.87	45.71	13.44			98.69	4.47	47.42	3.55	1.12	0.96	15.74	4.09	30.92
50	63.96	67.90	47.71			11.77	52.61	71.59	46.96	10.79	6.28	59.48	27.93	29.66
Mean/slide	49.03	38.27	34.35			43.90	34.05	38.14	34.73	27.04	15.11	21.55	20.03	23.36
Mean/animal														
Mean/dose														
							38.70	31.53		25.63			21.65	

Test item.		Dimethylhydrazine 20 mg/kg/day (x1)				Organ: DUODENUM Treatment: 26/09/2007			
Dose:		6535				6537			
Animal N°		236 A	236 B	236 C		237 A	237 B	237 C	6538
Slide No. BC-07-									
Code BC-07-14									
File No. BC-07-14									
No. of cell		J1.xls	J2.xls	J3.xls	% DNA in tail	F1.xls	F2.xls	F3.xls	% DNA in tail
1		73.50	67.34	45.91		89.60	16.72	75.31	
2		66.03	36.18	22.85		87.12	73.77	33.24	69.14
3		56.97	35.23	79.97		55.24	15.14	30.33	4.72
4		74.22	40.95	6.85		49.44	44.13	2.17	21.10
5		95.72	37.68	66.04		59.98	74.01	76.29	10.04
6		27.00	42.28	55.73		17.21	76.18	76.18	15.90
7		88.67	11.85	26.50		43.64	25.82	55.01	84.77
8		77.56	1.12	63.05		41.85	44.03	35.97	44.59
9		29.89	71.09	51.13		58.00	72.79	62.36	29.10
10		41.83	76.42	13.94		8.30	90.58	27.13	70.23
11		43.31	47.63	8.73		36.32	45.53	50.13	7.85
12		31.04	39.83	33.11		77.32	45.04	25.54	70.94
13		72.12	33.47	39.41		32.75	35.30	45.57	17.73
14		12.62	25.21	92.92		55.33	27.29	3.12	26.91
15		33.31	83.33	41.50		81.23	21.11	8.44	38.75
16		88.37	47.52	48.80		69.76	15.85	79.47	67.13
17		83.12	26.79	66.27		97.95	10.74	69.85	11.72
18		34.62	11.37	14.59		38.64	16.30	8.65	22.07
19		54.56	4.52	48.91		32.87	60.43	13.63	84.41
20		95.99	30.45	17.16		65.32	27.35	3.26	40.40
21		90.92	40.09	86.61		55.45	15.22	32.76	1.25
22		35.75	29.44	21.60		91.00	40.32	25.75	20.52
23		26.98	15.76	11.93		44.00	93.05	19.84	23.14
24		23.73	83.28	23.81		24.27	23.13	87.19	16.73
25		21.38	64.75	36.40		59.33	77.12	78.41	78.44
26		17.16	75.59	60.22		63.29	3.27	68.01	8.33
27		93.59	31.82	89.46		43.26	5.03	38.07	63.79
28		45.97	66.51	65.81		61.53	32.22	5.83	82.42
29		45.39	34.22	12.55		86.02	39.97	74.19	54.49
30		41.16	71.49	6.98		34.03	9.64	20.17	12.05
31		36.91	86.82	10.84		0.72	12.84	67.49	37.36
32		6.24	84.44	24.88		17.13	4.06	56.59	15.86
33		19.47	86.29	74.41		48.19	18.70	39.02	14.90
34		50.23	19.64	75.10		6.19	5.76	37.23	73.35
35		39.88	74.43	55.65		18.43	44.48	25.22	78.42
36		73.78	69.15	62.28		9.52	79.55	8.18	85.23
37		8.64	29.08	35.42		14.79	65.91	5.74	9.03
38		74.25	27.87	27.88		67.19	36.70	76.70	52.25
39		7.45	55.24	35.98		58.39	10.33	29.21	81.84
40		45.11	46.02	30.14		15.34	6.45	27.64	61.49
41		6.46	21.29	11.30		33.84	33.86	33.67	16.11
42		69.96	62.20	75.28		65.96	80.71	46.89	44.69
43		34.35	47.74	56.52		61.24	14.24	56.19	4.74
44		45.08	23.04	29.78		81.24	84.61	0.61	45.87
45		35.75	65.09	38.37		23.98	37.90	59.28	42.20
46		18.76	14.90	49.64		55.15	32.98	12.91	39.71
47		23.44	26.86	52.88		49.16	31.41	35.93	54.21
48		12.59	7.97	33.37		55.97	77.89	27.93	42.94
49		14.95	42.73	83.67		91.15	36.05	24.12	79.30
50		12.14	34.36	45.89		30.56	48.33	11.49	36.45
Mean/Slide		46.64	44.17	43.48		49.08	37.78	41.03	31.16
Mean/animal									38.98
Meandose			44.76				42.12		

## Appendix No. 13: Certificate of analysis



RHODIA OPERATIONS  
40 RUE DE LA HAIE COQ  
93306 AUBERVILLIERS CEDEX  
FRANCE

Manufacturing Plant  
RHODIA OPERATIONS  
RUE PROSPER MONNET  
69192 SAINT FONS  
FRANCE  
33 472 73 6000

Date  
15.05.2007  
Purchase order Item/Date  
Delivery Item/Date  
Order Item/Date  
Customer  
Truck number/Seal number

Material: Our / Your reference  
11459 CATECHOL FLAKES BIG BAG 1000 KG /  
PDS 220 FP CAT - 09/2000

This product complies with FMC requirements.  
\* Compliance guaranteed, skip testing.

Batch FPC0619301 / manufacturing date 15.07.2006 / Re-Test date 14.07.2008

Characteristic	Unit	Value	Limit Lower	Limit upper
Colour of acetic acid solution COLOURIMETER	HAZEN	485	-	1650
Assay TGA	%	99,7	99,5	-
Melting Point TGA	°C	104,7	103,7	-
Phenol HPLC	%	< 0,0100	-	0,1500
Hydroquinone * HPLC	%	< 0,0080	-	-
Dihydroxy 2,5 benzoquinone HPLC	%	0,1300	-	0,3000
Benzoic acid HPLC	%	< 0,0180	-	0,4000
Free Acidity in NaOH 0.1N/100g * POTENTIOMETRY	ml	8,4	-	50,0

batch released on : 17.07.2006 ;  
BERNADETTE LABAILLE, Laboratory Manager ; +33 472 736 179

B. LABAILLE 01/09/08

## Appendix No. 14: Coding slide Stomach

Organ                      STOMACH                      Coding No.    13

Doses in mg/kg/day (x2)	Animal No.	6512			6514			6511			6515		
0	Slide No. BC-07-	213 A	213 B	213 C	214 A	214 B	214 C	215 A	215 B	215 C	216 A	216 B	216 C
	Code BC-07-13	Q1	Q2	Q3	O1	O2	O3	E1	E2	E3	G1	G2	G3
	File No. BC-07-13	Q1.xls	Q2.xls	Q3.xls	O1.xls	O2.xls	O3.xls	E1.xls	E2.xls	E3.xls	G1.xls	G2.xls	G3.xls
	Animal No.	6518			6517			6520			6519		
400	Slide No. BC-07-	220 A	220 B	220 C	221 A	221 B	221 C	222 A	222 B	222 C	223 A	223 B	223 C
	Code BC-07-13	B1	B2	B3	K1	K2	K3	D1	D2	D3	S1	S2	S3
	File No. BC-07-13	B1.xls	B2.xls	B3.xls	K1.xls	K2.xls	K3.xls	D1.xls	D2.xls	D3.xls	S1.xls	S2.xls	S3.xls
	Animal No.	6524			6521			6522			6525		
200	Slide No. BC-07-	224 A	224 B	224 C	225 A	225 B	225 C	226 A	226 B	226 C	227 A	227 B	227 C
	Code BC-07-13	J1	J2	J3	C1	C2	C3	L1	L2	L3	R1	R2	R3
	File No. BC-07-13	J1.xls	J2.xls	J3.xls	C1.xls	C2.xls	C3.xls	L1.xls	L2.xls	L3.xls	R1.xls	R2.xls	R3.xls
	Animal No.	6527			6529			6526			6530		
100	Slide No. BC-07-	228 A	228 B	228 C	229 A	229 B	229 C	230 A	230 B	230 C	231 A	231 B	231 C
	Code BC-07-13	I1	I2	I3	P1	P2	P3	M1	M2	M3	H1	H2	H3
	File No. BC-07-13	I1.xls	I2.xls	I3.xls	P1.xls	P2.xls	P3.xls	M1.xls	M2.xls	M3.xls	H1.xls	H2.xls	H3.xls
	Animal No.	6534			6532			6531					
20 mg/kg/day (x1)	Slide No. BC-07-	217 A	217 B	217 C	218 A	218 B	218 C	219 A	219 B	219 C			
	Code BC-07-13	A1	A2	A3	F1	F2	F3	N1	N2	N3			
	File No. BC-07-13	A1.xls	A2.xls	A3.xls	F1.xls	F2.xls	F3.xls	N1.xls	N2.xls	N3.xls			

## Appendix No. 15: Coding slide Duodenum

Organ DUODENUM Coding No. 14

Doses in mg/kg/day (x2)													
0	Animal No.	6512			6514			6511			6515		
	Slide No. BC-07-	232 A	232 B	232 C	233 A	233 B	233 C	234 A	234 B	234 C	235 A	235 B	235 C
	Code BC-07-14	Q1	Q2	Q3	K1	K2	K3	D1	D2	D3	O1	O2	O3
	File No. BC-07-14	Q1.xls	Q2.xls	Q3.xls	K1.xls	K2.xls	K3.xls	D1.xls	D2.xls	D3.xls	O1.xls	O2.xls	O3.xls
400	Animal No.	6518			6517			6520			6519		
	Slide No. BC-07-	239 A	239 B	239 C	240 A	240 B	240 C	241 A	241 B	241 C	242 A	242 B	242 C
	Code BC-07-14	H1	H2	H3	M1	M2	M3	S1	S2	S3	N1	N2	N3
	File No. BC-07-14	H1.xls	H2.xls	H3.xls	M1.xls	M2.xls	M3.xls	S1.xls	S2.xls	S3.xls	N1.xls	N2.xls	N3.xls
200	Animal No.	6524			6521			6522			6525		
	Slide No. BC-07-	243 A	243 B	243 C	244 A	244 B	244 C	245 A	245 B	245 C	246 A	246 B	246 C
	Code BC-07-14	A1	A2	A3	P1	P2	P3	L1	L2	L3	E1	E2	E3
	File No. BC-07-14	A1.xls	A2.xls	A3.xls	P1.xls	P2.xls	P3.xls	L1.xls	L2.xls	L3.xls	E1.xls	E2.xls	E3.xls
100	Animal No.	6527			6529			6526			6530		
	Slide No. BC-07-	247 A	247 B	247 C	248 A	248 B	248 C	249 A	249 B	249 C	250 A	250 B	250 C
	Code BC-07-14	G1	G2	G3	I1	I2	I3	R1	R2	R3	B1	B2	B3
	File No. BC-07-14	G1.xls	G2.xls	G3.xls	I1.xls	I2.xls	I3.xls	R1.xls	R2.xls	R3.xls	B1.xls	B2.xls	B3.xls
20 mg/kg/day (x1)	Animal No.	6535			6537			6538					
	Slide No. BC-07-	236 A	236 B	236 C	237 A	237 B	237 C	238 A	238 B	238 C			
	Code BC-07-14	J1	J2	J3	F1	F2	F3	C1	C2	C3			
	File No. BC-07-14	J1.xls	J2.xls	J3.xls	F1.xls	F2.xls	F3.xls	C1.xls	C2.xls	C3.xls			

**Appendix No. 16: Historical data Stomach****HISTORICAL DATA OBTAINED IN STOMACH CELLS**

(from January 2007 to March 2007)

**Harvest time: 3-6 hours after the last treatment**

	<i>Median Min - Median Max</i>		
<b>SOLVENT CONTROL</b>	<b>1.46</b>	<b>-</b>	<b>4.71</b>
<b>POSITIVE CONTROL MNNG 20 mg/kg</b>	<b>3.59</b>	<b>-</b>	<b>8.54</b>

\*: median calculated on 150 cells

**Appendix No. 17: Historical data Duodenum****HISTORICAL DATA OBTAINED IN DUODENUM CELLS**  
**(from January 2007 to March 2007)**

**Two treatments at 24-hour interval with a sampling time 3 to 6 hours after the second treatment**

	<i>Median Min - Median Max</i>		
<b>SOLVENT CONTROL **</b>	<b>0.89</b>	<b>-</b>	<b>9.78</b>
<b>POSITIVE CONTROL</b> DMH (20 mg/kg)	<b>4.79</b>	<b>-</b>	<b>16.17</b>

*\*: median calculated on 150 cells*

**Appendix No. 18: Amendment No. 1 to Final Study Plan FSP-IPL 070402**



**Specimen to be returned  
dated and signed**

**AMENDMENT No. 1 TO THE STUDY PLAN FSP-IPL 070402**

Study title : In vivo COMET ASSAY IN THE RAT STUDY PERFORMED ON STOMACH  
and DUODENUM (two treatments, one sampling time)  
Sponsor : RHODIA  
Compound : CATECHOL  
Performed by : INSTITUT PASTEUR DE LILLE - Genetic Toxicology Laboratory -  
1, rue du Professeur Calmette - BP. 245 - 59019 LILLE CEDEX

The page 3 of the Final Study Plan will be modified as follows:

The control of concentrations in treatment solutions will be performed by:

Address for shipping :

Name: SGS Multilab  
Address: Technopôle du Madrillet  
65 rue Ettore Bugatti  
BP 90014  
76801 Saint Etienne du Rouvray cedex

Laboratory in charge of formulation analysis following Good Laboratory Practices

Name, address of the test site: SGS Multilab, Technopôle du Madrillet - 65 rue Ettore Bugatti - BP 90014  
76801 Saint Etienne du Rouvray cedex

Principal investigator:

Name, surname: Mr Gregory Bouillis

TEL: +33 (0) 02 35 07 91 87 FAX: +33 (0) 02 35 07 91 22 Email: [Gregory.Bouillis@sgs.com](mailto:Gregory.Bouillis@sgs.com)

Test site quality assurance

Name, surname: Ms SAPETA Corinne

TEL: +33 (0) 2 35 07 91 85 FAX: +33 (0) 2 35 07 91 92 Email: [corinne.sapeta@sgs.com](mailto:corinne.sapeta@sgs.com)

Test site manager

Name, surname: Mr Yvon GERVAISE

TEL: +33 (0)2 35 07 91 80 FAX: +33 (0)2 35 07 91 25 Email: [yvon.gervaise@sgs.com](mailto:yvon.gervaise@sgs.com)

All information concerning the procedures followed for analytical analysis, including analytical method, will be described in a Principal Investigator Phase Plan provided by **SGS Multilab**, validated by the study director, and included in a further amendment to the Study plan.

For Institut Pasteur de Lille

Date: 30/08/07

Date: 30/08/07

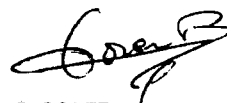
Date: 29/08/07



Professor D. MARZIN  
Test facility management



M. WATZINGER  
Study director



B. GOREZ  
Quality Assurance Unit

RHODIA

Date: 08/09/2007



Dr Arielle GARD  
Sponsor representative

Appendix No. 19: Amendment No. 2 to Final Study Plan FSP-IPL 070402



Specimen to be returned  
dated and signed

**AMENDMENT No. 2 TO THE STUDY PLAN FSP-IPL 070402**

Study title : *In vivo* COMET ASSAY IN THE RAT STUDY PERFORMED ON STOMACH  
and DUODENUM (two treatments, one sampling time)

Sponsor : RHODIA

Compound : CATECHOL

Performed by : INSTITUT PASTEUR DE LILLE - Genetic Toxicology Laboratory –  
1, rue du Professeur Calmette - BP. 245 - 59019 LILLE CEDEX

The dose of the positive control for the duodenum, dimethylhydrazine, was increased from 10 mg/kg to 20 mg/kg.

The Sponsor Representative Dr. Arielle GARD is replaced by Mr. Cyrille Bocquillod.

For Institut Pasteur de Lille  
Date: 20/08/08

Professor D. MARZIN  
Test facility management

Date: 25/08/08

Dr. M. WATZINGER  
Study director

Date: 20/08/08

B. GOREZ  
Quality Assurance Unit

For RHODIA  
Date: 03/09/08

Mr. Cyrille Bocquillod  
Sponsor representative

Appendix No. 20 : Amendment No. 3 to the Final Study Plan FSP-IPL 070402



Specimen to be returned  
dated and signed

**AMENDMENT No. 3 TO THE STUDY PLAN FSP-IPL 070402**

---

Study title : *In vivo* COMET ASSAY IN THE RAT STUDY PERFORMED ON STOMACH and  
DUODENUM (two treatments, one sampling time)

Sponsor : RHODIA

Compound : CATECHOL

Performed by : INSTITUT PASTEUR DE LILLE - Genetic Toxicology Laboratory -  
1, rue du Professeur Calmette - BP. 245 - 59019 LILLE CEDEX

---

**Rationale:**

The following text describes SGS Analytical Phase Plan ref n° BPL07-0029, relative to the determination of the concentration of Catechol in treatment formulations used in the *in vivo* comet assay in the rat.



## **SATELLITE STUDY DESIGN**

IDENTIFICATION NUMBER : BPL07-0029  
PAGE : 1/28  
REVISION : 0

### **STUDY PHASE TITLE**

#### **GLP STUDY OF AQUEOUS SOLUTIONS CONTAINING CATECHOL**

##### **Data requirement**

Internal method for catechol quantification by HPLC/UV  
(Assay Report RN07-12248)  
ASTM D4052-96 (MO-0225)

**Principal investigator**  
Grégory BOUILLIS

**Satellite Study Design completed on**  
December 05, 2007

##### **Test facility**

**INSTITUT PASTEUR DE LILLE**  
1, Rue du Professeur Calmette – BP  
245  
59019 LILLE Cedex  
FRANCE

##### **Test facility's reference** **(Study number)**

FSP-IPL070402 / CATECHOL /  
RHODIA

##### **Test site**

**SGS Multilab, Laboratory of**  
**Rouen**  
65, Rue Ettore Bugatti - BP 90014  
76801 SAINT ETIENNE DU  
ROUVRAY Cedex  
FRANCE

##### **SGS Multilab reference**

BPL07-0029

AMENDMENT No. 3 TO THE STUDY PLAN FSP-IPL 070402

**SGS**

**SATELLITE STUDY DESIGN**

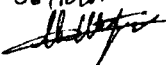
IDENTIFICATION NUMBER : BPL 07-0029  
 PAGE : 2/28  
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**APPROVAL FORM**

SGS MULTILAB, LABORATORY OF ROUEN

	VISA	DATE
Test Site Quality Assurance	Coffine SAPIET	December 05, 2007
Test Site Management	Yvon GERVAISE	December 05, 2007
Principal Investigator SGS Multilab, Laboratory of Rouen	Grégory BOUILLON	December 05, 2007

STUDY DIRECTOR: Name : Ms WATZINGER Malene  
 Company : INSTITUT PASTEUR DE LILLE  
 Address : 1, rue du Professeur Calmette  
 BP 245  
 59019 Lille Cedex

Date : 06/12/07  
 Visa : 

N.B.: This sheet has to be sent back filled out to begin the study phase.

## AMENDMENT No. 3 TO THE STUDY PLAN FSP-IPL 070402

<b>SGS</b>		<b>QUALITY FORM</b>	
<b>General Organisation Form GLP Studies</b>		Date : December 05, 2007 Date of application: 06/07/2007	N° IM-0029 L-2 Page : 3/28

STUDY DESCRIPTION ..... DETERMINATION OF CATECHOL CONTENT BY HPLC/UV	
N° OF STUDY ..... BPL07-0029	
STUDY DIRECTOR ..... Ms MALENE WATZINGER	
QUOTATION (AND DATE OF APPROVAL) : ..... DR07-2709 REVISION 1 DATED NOVEMBER 22, 2007 AND APPROVED DECEMBER 04, 2007	

<b>Staff :</b>	
UP/UA: SPECIFIC DETECTION BY HPLC (ORG01)	PERSON IN CHARGE OF CHECKS (GLP) : CORINNE SAPÉTA, AURÉLIE RENARD AND FRANCK BERCKER
PRINCIPAL INVESTIGATOR : GREGORY BOUILLIS	TECHNICAL STAFF : DOROTHÉE LAPÉRDIX, LOIC HERPIN AND GREGORY BOUILLIS
SUBSTITUTE : AUDE DE SLOOVERE	

<b>Test items</b>								
AQUEOUS SOLUTIONS								
<b>Field of application (matrix and range of content)</b>								
AQUEOUS SOLUTION CONTAINING CATECHOL FROM 5 TO 50 g/L								
<b>Test system</b>								
WILL BE DOCUMENTED IN THE FINAL SATELLITE REPORT								
<b>Reference documents</b>								
<input checked="" type="checkbox"/> PAQ/GLP EDITION N°7 DATED ON JANUARY 10, 2006 <input checked="" type="checkbox"/> QUALITY MANUAL EDITION N°10 DATED ON JUNE 22, 2007 <input checked="" type="checkbox"/> METHOD OR NORM : ASTM D4052-96 (MO-0225) <input checked="" type="checkbox"/> OTHER: FINAL REPORT RN07-12248 (OPERATING PROCEDURE AND DESCRIPTION OF VALIDATION OF CATECHOL QUANTIFICATION)								
<b>Planning</b>								
PREVISIONAL DATE OF BEGINNING: WEEK 50								
PREVISIONAL DATE OF ENDING: WEEK 52								
<input checked="" type="checkbox"/> Planning of GLP checks: according to the check list for study verification (IM-0027) <input checked="" type="checkbox"/> Validation for GLP study: <input type="checkbox"/> no <input checked="" type="checkbox"/> yes : <input type="checkbox"/> under GLP <input checked="" type="checkbox"/> outside GLP See study with reference RN07-12248 for validation of quantification method of catechol by HPLC/UV								
<b>Validation plan</b>								
(to complete if the validation is under GLP : This validation will also be detailed in the study plan without the initial form IM-0048)								
NB : if the validation is not under GLP, then form IM-0048 is completed after the validation meeting (and not the chart below), as specified in the general process of validation plan								
<table border="1"> <thead> <tr> <th>Test</th> <th>Matrix</th> <th>Number of tests</th> <th>Expected specifications</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Test	Matrix	Number of tests	Expected specifications				
Test	Matrix	Number of tests	Expected specifications					

PRINCIPAL INVESTIGATOR : GRÉGORY BOUILLIS	DIRECTOR OF INSTALLATION (GLP) : YVON GERVAISE
---	--

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**1. CONTEXT OF THE STUDY**

- Test facility: **INSTITUT PASTEUR DE LILLE**  
1, Rue du Professeur Calmette  
BP 245  
59019 LILLE Cedex  
FRANCE
  
- Study Director **Ms WATZINGER Malene**
  
- Principal Investigator : **Mr Grégory BOUILLIS**  
e-mail : gregory.bouillis@sgs.com  
Tel.: +33 2 35 07 91 87  
Fax: +33 2 35 07 91 22  
Chemical Formulations Customers Projects Manager
  
- Principal Investigator  
substitute : **Ms Aude DE SLOOVERE**  
e-mail : aude.de.sloovere@sgs.com  
Tel : +33 2 35 07 91 73  
Fax: +33 2 35 07 91 63  
Organic Chemistry Production Unit Manager
  
- Test site : **SGS Multilab, Laboratoire de Rouen**  
65, Rue Etienne Bugatti - BP 90014  
F-76801 SAINT ETIENNE DU ROUVRAY Cedex  
France  
Tel.: +33 2 35 07 91 91
  
- Test site manager : **Mr Yvon GERVAISE**  
Tel.: +33 2 35 07 91 80
  
- Test site manager :  
substitute **Mr Patrick BLANFUNE**
  
- Test site Quality assurance : **Ms Corinne SAPETA**  
e-mail : corinne.sapeta@sgs.com  
**Ms Aurélie RENARD**  
e-mail : aurelie.renard@sgs.com  
**Mr Franck BERCKER**  
e-mail : franck.bercker@sgs.com
  
- Quotation : **DR07-2709 Revision 1 dated November 22, 2007 and  
approved by the Sponsor on December 04, 2007.**
  
- Organisation of  
the study phase : **Cf Sheet IM-0029 dated on December 05, 2007**

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**- Abilities of the laboratory for the study phase :**

- *GLP by the G.I.P.C. according to the Directive 88/320 EEC :*
    - o Physico-chemical testing
    - o Environmental toxicity studies on aquatic and terrestrial organisms
    - o Studies on behaviour in water, soil and air ; bioaccumulation
    - o Residues studies
    - o Analytical and clinical chemistry
- Into practice of the French decree 98-1312 dated 31<sup>st</sup> December 1998

A copy of GLP acknowledgment will be supplied in addendum to the final report.

- *Laboratory accredited COFRAC under n° 1-0281*

**- Laboratory investigations :**

All tests bound in this programme will be carried out by SGS Multilab, Laboratory of Rouen.

**2. STUDY CONTENTS**

The aim of this study is the analysis of catechol in treatment solutions used in the in vivo comet assay performed on stomach and duodenum, in compliance with the principles of Good Laboratory Practices (GLP) according to the French decree (98-1312) and the application of the OECD principles of GLP to the organisation and management of multi-site studies (consensus document of the working Group on GLP, n°13). The density determination (MO-0225) will be also carried out on catechol solutions prepared by SGS Multilab to express the analysis of catechol with a fitted unit.

These analyses will relate to the determination of:

- Catechol content according to quantification method by HPLC/UV validated during the study referenced RN07-12248 (not under GLP scope).

Analyses will be done on test items referenced BPL07-0029.001, BPL07-0029.002, BPL07-0029.003, BPL07-0029.004, BPL07-0029.005, BPL07-0029.006, BPL07-0029.007 and BPL07-0029.008.

**3. TIME SCHEDULE**

Satellite study design schedule (indicative, if this study design is approved by the study director on week 50).

Study phase initiation	Issue of the satellite study design
Start of the experimental determination	Week 51
End of the experimental determination	Week 51
Issue of the Final satellite Report (Draft) to approval	Week 52

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**4. MEANS OF COMMUNICATION WITH THE STUDY DIRECTOR**

The Principal Investigator will communicate with the Study Director by phone or/and E-mail (Cf chapter 1).

The Principal Investigator will send to the Study Director raw results of this study phase (Excel file) in a timely manner.  
These results will be included in the final satellite report after Study Director's approbation.

**5. TEST ITEMS**

**Identification :** AQUEOUS SOLUTIONS CONTAINING CATECHOL received on October 30, 2007.

**Origin :** INSTITUT PASTEUR DE LILLE (IPL) (1, Rue du Professeur Calmette - BP 245 - 59019 LILLE Cedex - FRANCE).

**Amount required for the study phase :** Minimum 1 mL per test item.

**Test items identification :**

IPL's references	Amount (g)	SGS Multilab references	Description
FSP-IPL 070402 J1 Distilled water	2.685 (1)	BPL07-0029.001	Solvent (distilled water)
FSP-IPL 070402 J1 10 mg/mL	2.700 (1)	BPL07-0029.002	Catechol aqueous solution (10 mg/mL)
FSP-IPL 070402 J1 20 mg/mL	2.700 (1)	BPL07-0029.003	Catechol aqueous solution (20 mg/mL)
FSP-IPL 070402 J1 40 mg/mL	2.697 (1)	BPL07-0029.004	Catechol aqueous solution (40 mg/mL)
FSP-IPL 070402 J2 Distilled water	2.648 (1)	BPL07-0029.006	Solvent (distilled water)
FSP-IPL 070402 J2 10 mg/mL	2.715 (1)	BPL07-0029.006	Catechol aqueous solution (10 mg/mL)
FSP-IPL 070402 J2 20 mg/mL	2.726 (1)	BPL07-0029.007	Catechol aqueous solution (20 mg/mL)
FSP-IPL 070402 J2 40 mg/mL	2.744 (1)	BPL07-0029.008	Catechol aqueous solution (40 mg/mL)
Batch FPC0619301	139.9 (2)	BPL07-0029.009	Catechol flakes

(1) Gross weight weighed by SGS Multilab at reception.

(2) Gross weight weighed by SGS Multilab on December 05, 2007

Safety data sheet of catechol was sent by the sponsor and is supplied in appendix of this satellite study design

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**Storage:**

*During the study:* Storage in a freezer at -16°C, in the dark (the temperature will be followed each working day with IM-0137).

*After the study:* See 12.2. Information on archival storage for test items.

**Identification, manipulation, circulation :** In accordance with the sponsor's safety data sheet for this product.

**6. REFERENCE ITEMS**

Name	Catechol
Chemical Name (CA)	1,2-Benzenediol
CAS number:	120-80-9
Provider	FLUKA
Batch:	1325632
Purity:	99.99 %
Date of certificate:	February 07, 2007
Expiration date:	January 01, 2009
Appearance:	Fine crystals and flakes
Storage conditions:	In a refrigerator at 4°C and under argon
Safety instructions:	Do not take in, do not inhale and avoid skin and eye contact

The reference item will be used for external quantification.

A copy of the reference item certificate is supplied in appendix of this satellite study design.

MilliQ water (purified water for HPLC) will be used to check the oscillating densimeter used for density determination.

**7. REAGENTS (OR EQUIVALENT)**

MilliQ water (purified water for HPLC).

Acetonitrile.

Phosphoric acid.

Identity and origin of reagents used will be exactly documented in the final satellite report.

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**8. EQUIPMENTS (OR EQUIVALENT)**

- MillQ water purificator
- Usual laboratory glassware
- Ultrasonic bath
- High performance liquid chromatograph equipped with a UV diode array detector
- Column Hypersil GOLD C18, 150 x 4.6 mm (3 µm) and guard column with equivalent phase
- HV-0 45 µm Millex filter (PVDF)
- 20°C water bath
- Precision scale (0.01 mg)
- 1000 µL pipettor
- Refrigerator and freezer
- Oscillating densimeter

Identity of equipments used for this study phase will be documented in the final satellite report.

**9. DATA RECORDING**

The computer applications programs used to acquire and derive data for this study phase included Word, Excel and Empower Software.

Excel sheets used for this study phase are verified with a data set and cells are locked with a password by the quality assurance unit.

Software Empower supplied by Waters Corporation has been validated (certificate of software validation, product n° 667000437EN). Once more, every year, a standard operating procedure is carried out by SGS MultiLab Rouen, to check software results.

**10. AMENDMENTS/ DEVIATIONS (MODIFICATION FORMS)**

Each modification from the satellite study design, from the Final Study Plan IPL and from SGS MultiLab standard operating procedures' (SOP) will be documented, signed and dated by the Principal investigator and reported to the Study Director in a timely manner.

The Study Director will assess the impact of this modification on the quality and integrity of the study, and eventually elaborate an amendment. A summary of the modification(s) will be included in the satellite final report.

The amendment, prepared by the Study Director, will be signed and dated by the Principal investigator, the Test Site Management, the Study Director and the Sponsor Representative.

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**11. PROCEDURES****11.1. Operating procedure: Catechol quantification by HPLC/UV****11.1.1. Preparation of test items**

Tests will be realised by weighing about exactly 0.4 g of test item in a 50 mL volumetric flask, adding about 45 mL of MilliQ water, placing in the 20°C water bath for temperature equilibrating, adjusting to the mark with MilliQ water, filtering with a Millex filter and injecting in the chromatographic system, using external standardisation for quantification. Above procedure will be led 2 times for each test item to analyse (Test items BPL07-0029.002, BPL07-0029.003, BPL07-0029.004, BPL07-0029.006, BPL07-0029.007 and BPL07-0029.008).

**11.1.2. Preparation of reference items**

Catechol content in test items will be calculated from chromatographic peak area using a calibration curve with 5 reference item solutions prepared as followed:

- Weighing about exactly (with a precision of 0.01 mg) 50 mg of reference item twice in two 50 mL independent volumetric flasks. Dissolving the reference item in about 45 mL MilliQ water by placing it in an ultrasonic bath. Adjusting to the mark after equilibrating at 20°C in the water bath.
- Diluting 2 times (by pipetting 10 mL in a 20 mL volumetric flask), 10 times (by pipetting 5 mL in a 50 mL volumetric flask) and 50 times (by pipetting 2 mL in a 100 mL volumetric flask) one of these standard stock solutions.
- Diluting 4 times (by pipetting 5 mL in a 20 mL volumetric flask) and 20 times (by pipetting 5 mL in a 100 mL volumetric flask) the other one.
- All above dilutions will be realised using MilliQ water at 20°C in the 20°C water bath and then be injected in the chromatographic system.

**11.1.3. Preparation of eluant**

Eluant solutions will be prepared as followed:

- Water at 0.1% of phosphoric acid 85%: pipetting 1 mL (using 1000 µL pipettor) of phosphoric acid 85% in a 1000 mL volumetric flask and adjusting to the mark with MilliQ water.
- Acetonitrile at 0.1% of phosphoric acid 85%: pipetting 1 mL (using 1000 µL pipettor) of phosphoric acid 85% in a 1000 mL volumetric flask and adjusting to the mark with acetonitrile.

**11.1.4 Chromatographic conditions**

All reference item and test items solutions will be injected in high performance liquid chromatography (HPLC) coupled with UV diode array detector according to following conditions:

- Flow rate : 1 mL/min
- Wavelength : 278 nm
- Column : Hypersil GOLD C18, 250 x 4.6 mm (3 µm) and guard column with equivalent phase
- Temperature : 30°C
- Injection volume : 20 µL
- Retention time : About 10 minutes

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## • Eluant :

Time (min)	Acetonitrile at 0.1% of phosphoric acid (%)	Water at 0.1% of phosphoric acid (%)
0.0	5	95
15.0	5	95
15.1	90	10
18.0	90	10
18.1	5	95
25.0	5	95

The "sample list" will be begin with some reference item solutions injected several times, a solvent blank (MilliQ water), and the test item solutions injected twice, intercalating reference item regularly. At last, the "sample list" will end with some reference item solutions again.

Distilled water of day 1 (test item with reference BPL07-0029.001) will be injected as it is before injections of solutions of day 1 (test items with reference BPL07-0029.002, BPL07-0029.003 and BPL07-0029.004).

Distilled water of day 2 (test item with reference BPL07-0029.005) will be injected as it is before injections of solutions of day 2 (test items with reference BPL07-0029.006, BPL07-0029.007 and BPL07-0029.008).

## 11.1.5. Expression of results

Content of catechol in test items will be calculated with following formula:

$$[X]_j = \frac{(\text{Mean area test item } j - \text{Intercept}) \times V \times \text{purity} \times 10}{\text{Slope} \times m_j} \times \text{Density}$$

where :

$[X]_j$  = catechol content in test item solution preparation  $n^j$ , expressed in g/L.

Mean area test item  $j$  = mean peak area (for 2 injections) of the test item preparation  $n^j$ .

Intercept = Intercept of the calibration curve obtained with reference item solutions.

$V$  = final volume in L of the test item solution.

purity = purity of the reference item (%)

Slope = Slope of the calibration curve obtained with reference item solutions.

$m_j$  = weight of test item for preparation  $n^j$  in g.

Density = Density at 20°C of catechol solution with similar concentration (g/mL).

No result will be given for test items BPL07-0029.001 and BPL07-0029.005 because they are deionised water and will only be used to prove the absence of catechol in matrix blanks.

For test items BPL07-0029.002, BPL07-0029.003, BPL07-0029.004, BPL07-0029.006, BPL07-0029.007 and BPL07-0029.008, results will be given as the mean of 2 independent preparations.

All results will be rounded off to the second decimal.

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**11.2. Operating procedure: density determination**

In order to express results in g/L, density is required and must be determined.

Density at 20°C will be determined with an oscillating densimeter, according ASTM D4052-96 (MO-0225).

As the amount of test item is not enough to allow the measurement of density, it has been decided to prepare catechol aqueous solutions of similar concentrations and use the density of these solutions for the calculation of test items catechol concentration.

Catechol used for these preparations will be the one used for the validation of the method (see report RN07-12248), provided by RHODIA on August 30, 2007 and referenced for this study phase BPL07-0029.009.

A copy of this test item certificate is supplied in appendix of this satellite study design (document provided by RHODIA).

**11.2.1. Principle of density determination**

The principle is to introduce the solution in an oscillating sampling tube whose oscillation frequency modification due to the variation of tube mass is used, in association with calibration data, to determine the sample density.

**11.2.2. Preparation of catechol aqueous solutions**

3 catechol aqueous solutions will be prepared as followed.

- Weighing about exactly (with a precision of 0.01 mg) 500 mg of catechol flakes in a 50 mL volumetric flask (solution at about 10 mg/mL). Dissolving the catechol in about 45 mL distilled water by placing it in an ultrasonic bath. Adjusting to the mark after equilibrating at 20°C in the water bath.
- Weighing about exactly (with a precision of 0.01 mg) 500 mg of catechol flakes in a 25 mL volumetric flask (solution at about 20 mg/mL). Dissolving the catechol in about 20 mL distilled water by placing it in an ultrasonic bath. Adjusting to the mark after equilibrating at 20°C in the water bath.
- Weighing about exactly (with a precision of 0.01 mg) 1000 mg of catechol flakes in a 25 mL volumetric flask (solution at about 40 mg/mL). Dissolving the catechol in about 20 mL distilled water by placing it in an ultrasonic bath. Adjusting to the mark after equilibrating at 20°C in the water bath.

**11.2.3. Expression of density determination**

The result is given by the measurement oscillant densimeter and is rounded off to the third decimal.

The final result is expressed as the mean of two independent tests.

**11.3. Catechol stability study**

In order to ensure that there is no molecule degradation by freezing or in time, a determination of catechol content will be done on a catechol solution made for method validation (see report RN07-12248).

This aqueous solution of catechol at about 10 g/L has been made in the laboratory on October 05, 2007, using test item BPL07-0029.009. It has been used for precision study and 25 measures of catechol content have been realised on 3 different days (on October 05, 24 and 30, 2007). This solution has been kept in a freezer at less than -16°C.

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To prove the stability of catechol, a determination of catechol content in this solution will be realised at the same time than the determination of catechol content in test items. Preparations will be realised as described in chapter 11.3, and content will be calculate as described in chapter 11.1.5.

Solution of catechol will be considered as stable if the result does not differ than more than 5% from the mean of 25 previous measures (5% is the value provided by the FAO for storage procedure of pesticide formulations).

**11.4. Quality procedure**

The laboratory applied general and specific procedures described in the quality system in compliance with GLP requirements.

**12. FINAL SATELLITE REPORT**

The Final Satellite Report will be issued according to GLP regulations and will at least include the following items:

- complete general information (e.g. title, addresses, responsibilities and time schedule) as provided in this satellite study design,
- complete information about the reference item as provided in this satellite study design,
- signature of the Test site management and Principal Investigator,
- a statement of compliance with Good Laboratory Practice (GLP) signed by the Principal Investigator,
- a copy of the Test site's GLP certificate,
- a statement from the quality assurance unit signed by the Quality Assurance representative including inspection dates,
- information on archiving of material and documents,
- exact description of method and materials used in the course of this study phase,
- a summary of the relevant results,
- if necessary, a discussion of the results and of circumstances which might have influenced the quality and integrity of this study phase,
- the results tabulated.

The Study Director will receive the Draft final satellite report checked by the Quality Assurance Unit (QAU) for revision prior to release of the final satellite report and will, if necessary, add corrections.

After having given his written approval, the Study Director will receive one unbound original + 1 pdf file of the final satellite report.

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### 13. QUALITY PROGRAMME

Inspections are in accordance with Chapter II - 2 of the Quality Programme. They will be carried out by a person in charge of checks and according to the verification plan (Cf quality printed form IM-0027 "Check list of study verifications").

The study plan, subsequent amendments and the satellite study design will be inspected.

Results of these verifications will be included in a report (IM-0031 "Study report of verification").

During the study phase, periodic in-study audits will be driven according to the verification plan (Cf. quality printed form IM-0027 "Check list of study verifications"). Raw data will be audited.

When the study phase will be finished, a final satellite report will be edited and examined according to the check list final report (IM-0032).

All these verifications will be presented in the final satellite report to establish a statement on quality clarifying the inspections dates and the number of reports.

NB: the test site quality assurance unit will inform the principal investigator of each verification with the report (IM-0031). This will be signed by the principal investigator and the installation director of SGS Multilab Rouen, even if it is mentioned the term "Study Director".

Copies of the inspection reports will be sent to the Study Director in a timely manner.

### 14. INFORMATION ON ARCHIVAL STORAGE

#### 14.1. Documents

Documents referring to the G.L.P. study and study phase (copy of study plan and subsequent amendments, satellite study design, final satellite report, modification forms, raw data, check list) will be stored in a box by study in a locked cupboard in the basement of our Laboratory

The study phase will be archived after the totality of the study phase will be finished off for the Study Director and after his approbation.

After ten years, with the approbation of the Sponsor, all documents referring to the study phase will be destroyed or returned to the Sponsor.

Access: described in the GLP quality plan n°1.

Archivist: quality manager.

Documents referring to the staff are conserved in a locked cupboard in the office of the laboratory and during all the company existence.

Documents referring to other information are stored in the basement of our laboratory or in the analytical room for 10 years.

Documents referring to this study will be available for consultation by the Study Director at SGS Multilab Rouen.

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**14.2. Materials**

**Reference items:**

One specimen of each reference item will be stored for a period of time specified by analysis certificates.

**Test items:**

All samples of test items will be disposed of after the finalisation of the study phase (date of approbation of final satellite report). The Study Director will be informed with the form referenced MOD-0002.

Remaining samples of test items will be disposed of after analysis.

**14.3. Distribution of the satellite study design**

- |  |                      |
|--|----------------------|
| ✓ Study Director                                       | 1 original unbounded |
| ✓ QAU of SGS Multilab Rouen                            | 1 original           |
| ✓ A.U. Specific Detection by HPLC (SGS Multilab Rouen) | 1 copy               |

AMENDMENT No. 3 TO THE STUDY PLAN FSP-IPL 070402

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**SGS**

**SATELLITE  
STUDY  
DESIGN**

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**16. APPENDICES**

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## APPENDIX 1 : COPY OF CATECHOL MATERIAL SAFETY DATA SHEET (FRENCH VERSION) (1)

**Rhodia****FICHE DE DONNEES DE SECURITE**CATECHOL Page: 1 / 10  
Date: 26/10/96 Version: 7.04 Actualisé et complété version: 6.99**1 Identification du produit et de la société**

NOM du PRODUIT : CATECHOL  
Utilisation : Intermédiaire de synthèse.  
Initiateur de polymérisation pour monomères.  
Anticorrosif.  
(Pour plus de détails, se reporter à la fiche technique).

FOURNISSEUR : Polysar  
Nom : Rhodia Opérations [7]  
Adresse : 180 avenue Tolère - F-69487 LYON Cedex 08  
Téléphone : 33 4 37 34 86 86  
Télécopie : 33 4 37 34 86 99  
APPEL D'URGENCE : 04 78 70 00 00  
SPP/SLA : 91.46.42.94.99

**2 Composition / informations sur les composants**

>> SUBSTANCE  
Noms chimiques usuels : PYROCATECHOL >= 96.6 %  
Synonymes : Dihydroxy-1,2 benzaène.  
Cristal oligomère/monomère.  
Pyrocatecholène.

CAS : 120-80-9  
Représente présentement un danger : HYDROQUINONE (CAS: 123-31-6) : < 0.1 % [7]  
N° CE : 204-417-8 - Classification CE: Xn, N, R.22, 40, 41, 43, 50, 59

**3 Identification des dangers**

PRINCIPAUX DANGERS  
Effets observés sur la santé : Nocif par contact avec la peau et par ingestion.  
Sévérement irritant pour les yeux et la peau.  
Peut entraîner une sensibilisation par contact avec la peau. [7]

Dangers physiques et chimiques  
- Inflammable au contact  
: Soluble combustible.

Risques spécifiques : Selon la réglementation CE, ce produit est classé comme:  
- "NOCEUX" - "DANGEREUX".

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## APPENDIX 1 : COPY OF CATECHOL MATERIAL SAFETY DATA SHEET (FRENCH VERSION) (2)

**Rhodia****FICHE DE DONNEES DE SECURITE****CATECHOL**

Page 2 de 10

Date: 28/11/2006

Version: 7.04

Avis de remplissage version: 6.00

**4 Premiers secours**

Inhalation	: Soulever le sujet de l'exposition. Mettre au repos. Consulter éventuellement un médecin. Montrer cette fiche au médecin. [7]
Contact avec la peau	: Oter tout vêtement ou chaussure souillés. Laver immédiatement, abondamment et de manière prolongée (15 min au moins). En cas d'irritation (rougeur, irritation, ...), consulter un médecin. Montrer cette fiche au médecin. [7]
Contact avec les yeux	: Rincer à l'eau courante immédiat et prolongé en maintenant les paupières bien ouvertes (15 minutes au moins). Consulter un médecin en cas d'irritation persistante. Montrer cette fiche au médecin. [7]
Ingestion	: Ne JAMAIS tenter de faire vomir. Ne rien donner à boire. Consulter éventuellement un médecin. Montrer cette fiche au médecin. [7]
Autres informations	: Récupérer les vêtements souillés dans un sac étanche pour décontamination ultérieure. Utiliser les équipements de protection appropriés pour traiter une personne contaminée. [7]

**5 Mesures de lutte contre l'incendie**

Moyens d'extinction	: Eau pulvérisée/Oxygène de carbone (CO2)/Mousse
- Apprêtée	: Jet d'eau bête.
- Déconseillée	: En cas d'incendie à proximité, utiliser les agents d'extinction adaptés.
Dangers spécifiques	: Lors de la combustion/Dégagement de gaz toxiques.
Méthodes particulières d'intervention	: Utiliser les moyens adaptés pour combattre les incendies éventuels. Rester du côté opposé au vent. Evacuer le personnel à l'air des fumées. Retenir à l'eau pulvérisée les températures exposées à la chaleur.
Procédures des interventions	: Boîtes et équipement de protection, étanche. Appareil de protection respiratoire isolant autonome.

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## APPENDIX 1 : COPY OF CATECHOL MATERIAL SAFETY DATA SHEET (FRENCH VERSION) (3)

**Rhodia****FICHE DE DONNEES DE SECURITE****CATECHOL**

Page 3 de 10

Date: 28/11/2008

Version: 7.04

Annulé et remplacé version: 6.00

**6 Mesures en cas de dispersion accidentelle**

Précautions individuelles	: Eviter le contact avec la peau et les yeux. Épandage important: Éviter le produit sur la voie publique, alerter le danger et (si/le) prévenir les autorités (Police ou Gendarmerie, Pompiers). Ne PAS appuyer l'ACR au vent. Ne pas respirer les poussières. Ne PAS laisser le produit se répandre dans l'environnement. Ne pas respirer les vapeurs. Équipement de protection: - appareil de protection respiratoire filtrant. - gants appropriés. - bottes imperméables. - protection des yeux et du visage (casque « visage »). Baliser la zone d'épandage et en interdire l'accès aux personnes non autorisées. Signaler le danger. Intervention limitée au personnel qualifié muni des protections appropriées. Vérifier mécaniquement la zone de déversement, en prévenant la formation de mélanges explosifs avec l'air.
Précautions pour la protection de l'environnement	: Ne pas laisser le produit se répandre dans l'environnement. Éviter et limiter l'épandage (produit dangereux pour l'environnement).
Méthodes de nettoyage - Réamplification	: Réamplifier le produit au maximum. Récupérer mécaniquement le produit. Recueillir le produit dans un récipient de secours: - conformément à l'étiquette. - en plusieurs. Conserver le produit récupéré pour élimination ultérieure.
- Nettoyage/décontamination	: Laver avec de l'eau savonneuse (2 à 5 %). Puis laver à grande eau. Récupérer les eaux de lavage pour élimination ultérieure.
- Élimination	: Pour l'élimination des résidus ou résidus solides, se reporter au § 12: "Considérations relatives à l'élimination".

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## APPENDIX 1 : COPY OF CATECHOL MATERIAL SAFETY DATA SHEET (FRENCH VERSION) (4)

**FICHE DE DONNEES DE SECURITE**

CATECHOL

Page 4 de 10

Date: 30/11/2006

Version: 7.04

Annexe al formulaire européen: 6.00

## 7 Manipulation et stockage

### MANIPULATION

#### Measures techniques

- : Captation des poussières (Aspiration).
- Prévoir l'utilisation en abîme fermé.
- Sous le bon des équipements de travail.

#### Précautions à prendre

- : Éviter le contact avec l'air.
- Éviter la formation ou la dispersion de poussières dans l'atmosphère.
- Éviter tout contact direct avec le produit.

#### Conseils d'utilisation

- : Éviter les accumulations de poussières.
- Rappeler les conditions d'emploi (se référer à la notice technique).

### STOCKAGE

#### Measures techniques

- : Le sol de dépôt doit être imperméable.
- Prendre toutes dispositions nécessaires pour éviter le rejet accidentel du produit (hors les agents et dans les eaux d'écoulement, en cas de rupture des récipients ou des systèmes de transfert).

#### Conditions de stockage

##### - Recommandations

- : Pour garantir la qualité et les propriétés du produit, conserver:
  - à l'abri de l'air,
  - à l'abri de la lumière,
  - le récipient bien fermé et à l'abri de l'humidité,
  - à l'abri de toute source d'ignition.

#### Matériaux incompatibles

- : Acides.
- Alcalis et produits oxydants.

#### Conditions d'emballage

- : Conserver le produit soigneusement dans l'emballage d'origine.
- Conditionner soigneusement avec des plastiques inertes.
- Sans papier.

#### Matériaux d'emballage

##### - Recommandations

- : Polyéthylène.
- Verre teinté.
- Papier.

##### - Contre-indications

- : Aluminure et ses dérivés.

## 8 Contrôle de l'exposition / protection individuelle

### Measures d'ordre technique

- : Opérer en système clos.
- Capturer les poussières à leur point d'émission.
- Sous le bon des équipements de travail.
- Assurer une bonne ventilation du poste de travail.

#### Paramètres de contrôle

##### Valeurs limites d'exposition

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## APPENDIX 1 : COPY OF CATECHOL MATERIAL SAFETY DATA SHEET (FRENCH VERSION) (6)

**Rhodia****FICHE DE DONNEES DE SECURITE**

CATECHOL		Page 5 de 10
Date: 28/11/2004	Version: 2.04	Ajouté et corrigé version: 6.00
- Valeurs limites (France)	Catechol VLE: 20 mg/m <sup>3</sup> (8 ppm) HYPEROXYDANT VLE: 2 mg/m <sup>3</sup>	
- Valeurs limites (U.S.A. / A.C.G.I.R.)	Catechol TLV (TWA): 20 mg/m <sup>3</sup> (8 ppm) Pour l'hyperoxydant: TLV (TWA): 2 mg/m <sup>3</sup>	
Équipements de protection individuelle	Appareil de protection respiratoire filtrant anti-particules. En cas de libération de vapeurs: Appareil de protection respiratoire autonome isolant.	
- Protection des yeux	Gants de protection en PVC. Surbrassards de protection isolant. Gilet de protection long, recouvrant par dessus les manches.	
- Protection des yeux	Lunettes de sécurité + écran facial.	
- Protection de la peau et du corps	Vêtements de protection. En cas de risque de projection de liquide ou de libération de vapeurs: Combinaison en HYPALON ou à défaut en PVC.	
Moyens collectifs d'urgence	Déchamps de sécurité. Perches isolantes. Équipements et matériel de secours immédiatement accessibles avec système d'alimentation.	
Mesures d'urgence	Se laver les mains après toute manipulation. Ne PAS fumer, manger ou boire sur le lieu de travail. Séparer les vêtements de travail des vêtements de ville.	

**9 Propriétés physiques et chimiques**

ASPECT	
- Etat physique	: Solide. Liquide au-dessus de 105°C.
- Forme	: Cristaux.
- Couleur	: Blanc/brun.
- Odeur	: Solide / phénolique.
pH	: 3.2 (solution saturée à 10 g/100ml).
Températures caractéristiques	
- Fusion	: 103,8-105°C. [1]
- Effluents	: 245°C. (à pression normale : 1013 hPa) 178°C. (à 100 hPa) 154°C. (à 0,7 hPa).
Caractéristiques d'inflammabilité	
- Point d'écoulement	: 127°C (Coupé fermé, selon norme NF T 60103).
- Température d'auto-inflammation	: 510°C (Température d'auto-inflammation spontanée).
Propriétés oxydantes	: Non oxydant selon les critères CE.
Caractéristiques d'explosivité	

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## APPENDIX 1 : COPY OF CATECHOL MATERIAL SAFETY DATA SHEET (FRENCH VERSION) (8)

**Rhodia****FICHE DE DONNÉES DE SECURITE**

CATECHOL		Page 6 de 10
Date: 28/11/2004	Version: 7.04	Angle et graphique version: 6.00
Limite d'exposition dans l'air	: (Vapeur).	
- Inhalation	: 1.97 g (Métro).	
Pression de vapeur	: 0.04 kPa, à 20°C.	
	7.7 kPa, à 154°C.	
	2.7 kPa, à 134°C.	
Densité de vapeur (air = 1)	: 3.8.	
Densité relative (eau = 1)	: 1.371 à 20°C. (Détermination effectuée sur le produit solide après fusion)	
Masse volumique apparente	: 0.8 - 0.8 kg/m <sup>3</sup> (Produit non tassé).	
Solubilité	:	
- dans l'eau	: Facilement soluble.	
	275 g/l à 20 °C.	
	500 g/l à 50 °C.	
- dans les solvants organiques	: Facilement soluble dans:	
	- méthanol, 500 g/l à 20 °C.	
	- éthanol (96%), 500 g/l à 20 °C.	
	- Acétone, 500 g/l à 20 °C.	
	- chloroforme, 10 g/l à 20 °C.	
	- Pour solubilité dans:	
	- tétrahydrofur de carbone, 1 g/l à 20 °C.	
Coefficient de partage n-Octanol/eau	: 0.56 (log POW)	
<hr/>		
<b>10 Stabilité et réactivité</b>		
Stabilité	: Stable à température ambiante.	
Réactions dangereuses	:	
- Mélanges à éviter	: - bases.	
	- oxydants.	
- Produits de décomposition dangereux	: Par combustion ou par décomposition thermique (pyrolyse), libère des vapeurs toxiques.	
	(Phénol), (Oxyde de carbone - CO + CO <sub>2</sub> ).	
<hr/>		
<b>11 Informations toxicologiques</b>		
Toxicité aiguë	: CL 5 Ingestion, 5 IC 50 2.8 mg/kg (Rat) [7] (Données subchroniques).	
	Rat: par ingestion de 100 mg/kg.	
	DL 50 souris: 100 mg/kg (Rat) [7]	
	Propriétés toxiques non précises	
	Rat: en test d'ingestion.	
	DL 50 souris: 200 mg/kg	
	(Données subchroniques).	

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## APPENDIX 1 : COPY OF CATECHOL MATERIAL SAFETY DATA SHEET (FRENCH VERSION) (7)

**Rhodia****FICHE DE DONNEES DE SECURITE****CATECHOL**

Page: 7 de 10

Date: 28/11/2006

Version: 7.04

Annule et remplace version: 6.00

**Effets connus**: Sévèrement irritant par application cutanée chez le lapin.  
Sévérement irritant par application oculaire chez le lapin.**Sensibilisation**: Peut entraîner une sensibilisation par contact avec le peau.  
(Cibex®) [?]  
(Données bibliographiques).**Toxicité par administration répétée**: Toxicité par exposition répétée (28 jours)  
Dose sans effet grave observé (NOAEL) : 33 mg/kg/jour [?]  
Toxicité digestive (rat)  
(Données bibliographiques).**Effets spécifiques****- Carcinogénicité**

: Par ingestion répétée de fortes doses, provoque des tumeurs de l'estomac des rats, souris, hamsters. Mode d'action considéré comme non pertinent pour l'homme. [?]

**- Mutagénicité**: Des résultats contradictoires ont été observés dans différentes études Des mutations positives ont été observées en cours d'évaluation [?]  
(Données bibliographiques).**- Toxicité pour la reproduction**: par ingestion (rat)  
aucune altération de la fertilité n'a été observée [?]  
(Données bibliographiques).**12 Informations écologiques****MOBILITE**

Comportement stable du produit

: Comportement stable ultime du produit: EAU.

**BIODGRADABILITE**

Dégradation abiotique

: Demi vie : 0,845 jours. (Données bibliographiques).

- Photolyse

**BIODGRADABILITE**

- Biodégradabilité écotoxique

: Facilement biodégradable. (Données bibliographiques).

**BIOACCUMULATION**

Coefficient de partage n-Octanol/eau

: Non potentiellement bioaccumulable. (Données bibliographiques). Se reporter au § 9 pour les données chiffrées.

**ECOTOXICITE**

Effets sur les organismes aquatiques

: CL 50 (Poisson: *Oreochromis zillisch*) / 96h: 0,9 mg/L [?]  
CE 50 (Algues d'eau douce: *Chlorella vulgaris*) / 96 h: 22 mg/L [?]  
(Données bibliographiques).  
CE 50 (*Daphnia magna*) / 24 h : 2,1 mg/L. (Rapports toxicologiques non publiés)

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## APPENDIX 1 : COPY OF CATECHOL MATERIAL SAFETY DATA SHEET (FRENCH VERSION) (8)

**Rhodia****FICHE DE DONNÉES DE SECURITE**

CATECHOL

Page 1 de 10

Date: 28/11/2006

Version: 7.01

Année et remplissage version: 6.66

**13 Considérations relatives à l'élimination****RESIDU DU PRODUIT**

Interdictions

- : Ne pas laisser le produit se disperser dans l'environnement.
- : Interdiction de mise en décharge.
- : Inclure dans une installation autorisée.

Destruction/élimination

**EMBALLAGES SOUILLES**

Interdictions

- : Interdiction de mise en décharge.

Décontamination/nettoyage

- : Vider complètement les emballages avant décontamination.

Destruction/élimination

- : Inclure dans une installation autorisée.

**REMARQUE**

- : L'attention de l'utilisateur est attirée sur la possible existence de contraintes et de prescriptions locales, relatives à l'élimination, le cas échéant.

**14 Informations relatives au transport****REGLEMENTATIONS INTERNATIONALES**

Voies terrestres

- Rail/Route (RIDADR)

- : N° ONU : 2811
- : Désignation officielle de transport (Rimé) : TOXIC SOLID,
- : CATECHOL, N.O.S. (CATECHOL)
- : Étiquetage: 6.1.
- : Groupe d'emballage: II.
- : Classement global: 6.1
- : N° d'identification du danger: 60

Voie maritime (CMR/MDG)

- : N° ONU: 2811
- : Désignation officielle de transport (Rimé) : TOXIC SOLID,
- : CATECHOL, N.O.S. (CATECHOL)
- : Étiquetage: 6.1.
- : Groupe d'emballage: II.
- : Classement global: 6.1
- : Population exposée: 1000
- : Risque de réaction (R): F-A, S-A.

Voie aérienne (DACH/ATA)

- : N° ONU: 2811
- : Désignation officielle de transport (Rimé) : TOXIC SOLID,
- : CATECHOL, N.O.S. (CATECHOL)
- : Étiquetage: 6.1.
- : Groupe d'emballage: II.
- : Classement global: 6.1
- : Avion Passagers: Interdiction d'emballage: 610 Quantité: 100 kg
- : Avion Cargo : Interdiction d'emballage: 610 Quantité: 200 kg

## AMENDMENT No. 3 TO THE STUDY PLAN FSP-IPL 070402

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## APPENDIX 1 : COPY OF CATECHOL MATERIAL SAFETY DATA SHEET (FRENCH VERSION) (8)

**Rhodia****FICHE DE DONNEES DE SECURITE****CATECHOL**

Page 9 de 10

Date: 23/1/2004

Version: 3.04

Ajouts et remplissage version: 4.00

**REMARQUE**

: Les prescriptions réglementaires relatives à l'emballage, sont celles en vigueur le jour de l'impression de la SDS.  
 Ainsi, corrigé-tout d'un éventuel impact possible des réglementations relatives à l'emballage des matières dangereuses, il est conseillé de s'assurer de leur validité auprès de votre agence autorisée.

**15 Informations réglementaires****ETIQUETAGE**

Réglementation CE

: Etiquetage réglementaire obligatoire des substances dangereuses: **DANGEREUX**

- Identification du produit dangereux

: Nom chimique de la substance : CATECHOL  
 NF CE : 204-627-8

- Symboles et indications de danger

: - H036P (Xn)

- Phrases R

: R 37/38: Irrite par contact avec la peau et par ingestion.

- Phrases S

: S 22: Ne pas respirer les poussières.  
 S 28: En cas de contact avec les yeux, laver immédiatement et abondamment avec de l'eau et consulter un spécialiste.  
 S 37: Porter des gants appropriés.**NOTE**

: Les informations réglementaires reprises dans cette section rappellent uniquement les principales prescriptions spécifiques applicables au produit objet de la FDS. L'attention du Fournisseur est attirée sur la possibilité existence d'autres dispositions complémentaires prescrites. Il est recommandé de se référer à toutes mesures ou dispositions, internationales, nationales ou locales pouvant s'appliquer.

**16 Autres informations**

Types d'utilisation

- Utilisations autorisées

: Produit destiné exclusivement à un usage industriel.

Formule chimique

: C6 H6 O2

Masse molaire

: 110.11g

Nombres d'enregistrement

: Inscrit dans l'inventaire chinois inscrit dans l'inventaire EINECS, inscrit dans l'inventaire JECFA, inscrit dans l'inventaire canadien (CEPA DSL), inscrit dans l'inventaire AEC, inscrit dans l'inventaire de l'Union européenne (REACH), inscrit dans l'inventaire japonais (PICOP).

Phrases R (n° 2 &amp; 3)

:



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## APPENDIX 2 : COPY OF TEST ITEM BPL07-0029.009 (CATECHOL FLAKES) CERTIFICATE (FRENCH VERSION)



RHODIA OPERATIONS  
40 RUE DE LA HAIE COQ  
93306 AUBERVILLIERS CEDEX  
FRANCE

usine de fabrication  
RHODIA OPERATIONS  
RUE PROSPER MORRET  
69192 SAINT FONS  
FRANCE  
33 472 73 6000

**Certificat d'analyse**

Date  
23.06.2007  
Poids de référence/Date

Poids livrés/Date

Poids d'essai/Date

Client

N° immobilisation/° place

Article : notre / votre désignation  
11459 CATECHOL FLAKES BIG BAG 1000 KG /

Cet article a été produit conformément aux exigences FMC.  
\* Conformité garantie, résultat en fréquence.

Lot FPC0619301 / date de fabrication 15.07.2006 / date de ré-analyse 15.07.2008

Caractéristique	Unité	Valeur	Limite inférieure	Limite supérieure
Coloration aci. acide. acide % COLORIMETRIE	HAZEN	488	-	1650
Titre ACD	%	99,7	99,5	-
Point de Fusion ACD	°C	104,7	103,7	-
Phénol CLAP	%	< 0,0100	-	0,1900
Hydroquinone * CLAP	%	< 0,0080	-	-
D.H.S.Q. CLAP	%	0,1300	-	0,3000
Acide benzoïque CLAP	%	< 0,0180	-	0,4000
Acide libre NaOH 0.1N/100g * FORMALDEHYDE	ml	8,4	-	80,0

Lot libéré le : 17.07.2006 ;  
Bernadette LAFAYE, Responsable Laboratoire ; +33 472 736 179

## AMENDMENT No. 3 TO THE STUDY PLAN FSP-IPL 070402

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## APPENDIX 3 : COPY OF REFERENCE ITEM (CATECHOL) CERTIFICATE

**SIGMA-ALDRICH****Certificate of Analysis**

Product Name	Pyrocatechol, puriss., crystallized, ≥99.5% (HPLC)
Product Number	15880
Product Brand	Pure
CAS Number	120-80-9
Molecular Formula	$C_6H_4-1,2-(OH)_2$
Molecular Weight	110.11

TEST	LOT 4828632 RAREFATS
APPEARANCE (COLOR)	COLORLESS
APPEARANCE (FORM)	FINE CRYSTALS AND FLAKES
PURITY (HPLC AREA %)	99.99 % m
MELTING POINT	105 °C
SOLUBILITY (COLOR)	COLORLESS
SOLUBILITY (TURBIDITY)	CLEAR (<1.5 NTU)
SOLUBILITY (METHOD)	1 g IN 10 ML MECH
CARBON CONTENT	65.62 %
HYDROGEN CONTENT	5.32 %
INFRARED SPECTRUM	CHARACTERISTICS
DATE OF QC RELEASE	07/08/07
DATE OF RECOMMENDED RETEST	24/09

Sigma-Aldrich guarantees the "Sales Specification" values only, non-specified tests may be included as additional information. The current "Sales Specification" sheet is present on our website. For further inquiries, please contact our Technical Service. Sigma-Aldrich warrants that the products conform to the information contained in the data sheet. Sigma-Aldrich does not warrant, purchase or sell products for the purpose of the preparation of the product for the particular use. The values given on the "Certificate of Analysis" are the results determined at the time of analysis.

Dr. Gert van Loek, Manager  
Quality Control  
Buchs, Switzerland

AMENDMENT No. 3 TO THE STUDY PLAN FSP-IPL 070402

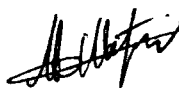
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For Institut Pasteur de Lille  
Date: 02/09/08



Professor D. MARZIN  
Test facility management

Date: 02/09/08



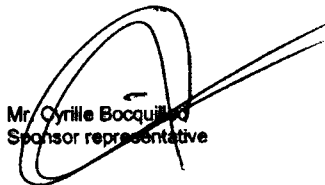
Dr. M. WATZINGER  
Study director

Date: 02/09/08



B. GOREZ  
Quality Assurance Unit

For RHODIA  
Date: 11/03/08



Mr. Cyrille Bocquillon  
Sponsor representative

Appendix No. 21: Amendment No. 4 to the final study plan FSP-IPL 070402



Specimen to be returned  
dated and signed

**AMENDMENT No. 4 TO THE STUDY PLAN FSP-IPL 070402**

Study title : In vivo COMET ASSAY IN THE RAT STUDY PERFORMED ON STOMACH  
and DUODENUM (two treatments, one sampling time)

Sponsor : RHODIA

Compound : CATECHOL

Performed by : INSTITUT PASTEUR DE LILLE - Genetic Toxicology Laboratory -  
1, rue du Professeur Calmette - BP. 245 - 59019 LILLE CEDEX

Dr Fabrice NESSLANY replaces the Study Director Dr Malene WATZINGER and Dr Sophie SIMAR replaces the Deputy Study Director Dr Fabrice NESSLANY. These modifications applied to all the parts of the study plan and the analytical satellite study design where the name of the Study Director and the Deputy Study Director are mentioned.

For Institut Pasteur de Lille  
Date: 10/10/08

Date: 10/10/2008

Date: 10/10/08

Dr. Daniel MARZIN  
Test facility management

Dr. Fabrice NESSLANY  
Study director

Ms. Brigitte GOREZ  
Quality Assurance Unit

RHODIA  
Date: 10/15/2008 (15 October 2008)

Mr. Cyrille Bocquillon  
Sponsor representative

Appendix No. 22 : Control of concentration in dosing formulations



## **FINAL SATELLITE REPORT**

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### **STUDY PHASE TITLE**

**GLP STUDY OF AQUEOUS SOLUTIONS CONTAINING CATECHOL**

#### **Data requirement**

Internal method for catechol quantification by HPLC/UV  
(Assay Report RN07-12248)  
ASTM D4052-96 (MO-0225)

#### **Principal Investigator**

Grégory BOUILLIS

#### **Study completed on**

January 14, 2008

#### **Test facility**

**INSTITUT PASTEUR DE LILLE**  
1, Rue du Professeur Calmette – BP  
245  
59019 LILLE Cedex  
FRANCE

#### **Test facility's study number**

FSP-IPL070402 / CATECHOL /  
RHODIA

#### **Test site**

**SGS Multilab, Laboratory of**  
**Rouen**  
65, Rue Ettore Bugatti - BP 90014  
76801 SAINT ETIENNE DU  
ROUVRAY Cedex  
FRANCE

#### **SGS Multilab reference**

BPL 07-0029

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**APPROVAL FORM**

SGS MULTILAB, LABORATORY OF ROUEN

	VISA	DATE
Test Site Quality Assurance	Corinne SAPIET	January 14, 2008
Test site Management	Yvon GERVAISE	January 14, 2008
Principal Investigator SGS Multilab, Laboratory of Rouen	Grégory BOUILLIS	January 14, 2008

STUDY DIRECTOR :

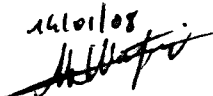
Name : Ms WATZINGER Malene

Company : INSTITUT PASTEUR DE LILLE

Adress : 1, rue du Professeur Calmette  
BP 245  
59019 Lille Cedex

Date

Visa

: 14/01/08  
: 

N.B. : This sheet must be completed.



## **FINAL SATELLITE REPORT**

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### **GOOD LABORATORY PRACTICE COMPLIANCE STATEMENT**

The reported study phase was performed at the laboratory SGS Multilab - Rouen in accordance with the valid procedures at the laboratory.

I, the undersigned, Grégory BOUILLIS, Principal investigator, certify that the study phase mentioned above was conducted in compliance with the principles of Good Laboratory Practices (GLP) as defined in the French Decree n°98-1312 dated on 31<sup>st</sup> December 1998.

The validity date of our GLP diploma expired on May 29<sup>th</sup>, 2007. We have asked to the French authorities in order to have a continuation until the audit date programmed without any break of our GLP acknowledgement.

Date : January 14, 2008

Visa :

A handwritten signature in black ink, appearing to be 'G. Bouillis', written over a series of horizontal lines.



## FINAL SATELLITE REPORT

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### QUALITY ASSURANCE STATEMENT

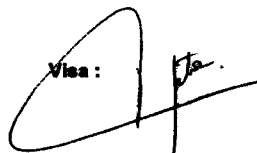
I, the undersigned, Corinne SAPETA, person in charge of the quality assurance unit, certify that the study phase mentioned above was verified in accordance with the French Decree n° 98-1312 dated 31<sup>st</sup> December 1998.

The final phase report was audited according to the appropriate standard operating procedure and provides an accurate record of the results obtained.

<u>Date of inspection</u>	<u>Type of inspections</u>	<u>Date reported to Test site management and Principal Investigator</u>
November 16, 2007	Satellite Study design (draft 1)	RV n°1, November 16, 2007
December 05, 2007	Satellite Study design (draft 2)	RV n°2, December 05, 2007
December 05, 2007	Satellite Study design rev 0	RV n°3, December 05, 2007
December 17, 2007	Study, installation and process	RV n°4, December 17, 2007
December 19, 2007	Study and process	RV n°5, December 19, 2007
December 27, 2007	Satellite Final report (Draft 1)	RV n°6, December 27, 2007
January 09, 2008	Satellite Final report (Draft 2)	RV n°7, January 09, 2008
January 14, 2008	Satellite Final report rev 0	RV n°8, January 14, 2008

Dates of reporting to the Study Director (IPL): November 16, 2007, December 05, 2007, December 06, 2007, December 19, 2007, December 20, 2007, December 27, 2007, January 09, 2008 and January 14, 2008.

Person in charge of quality assurance unit  
Date : January 14, 2008

Visa : 

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**ABSTRACT AND INTRODUCTION**

The aim of this study was the determination of catechol content in treatment solutions used in vivo comet assay performed on stomach and duodenum, in compliance with the principles of Good Laboratory Practice (GLP) according to the French decree (98-1312) and the application of OECD principles of GLP to the organisation and management of multisites studies (consensus document of the working Group on GLP, n°13). These analyses were done by carrying out the HPLC/UV quantification method validated during the study RN07-12248 (not under GLP scope).

The test items were sent by INSTITUT PASTEUR DE LILLE (1, rue du Professeur Calmette, BP 245, 59019 Lille cedex, FRANCE) and received at the laboratory on October 30, 2007. They were identified by SGS Multilab Rouen BPL07-0029.001, BPL07-0029.002, BPL07-0029.003, BPL07-0029.004, BPL07-0029.005, BPL07-0029.006, BPL07-0029.007 and BPL07-0029.008.

Catechol content has been determined by weighing about exactly 0.4 g of test item in a 50 mL volumetric flask, adding about 45 mL of MilliQ water, placing in the 20°C water bath for temperature equilibrating, adjusting to the mark with MilliQ water, filtrating with a Millex filter and injecting in the chromatographic system, using external standardisation for quantification.

Above procedure was led 2 times for each test item to analyse.

Results are described below:

Sponsor's test item reference FSP-IPL 070402	SGS Multilab test item reference	Catechol content (mg/mL)	Difference (%)
Distilled water J1	BPL07-0029.001	No chromatographic peak detected	-
10 mg/mL J1	BPL07-0029.002	9.77	-2.3
20 mg/mL J1	BPL07-0029.003	19.4	-3.0
40 mg/mL J1	BPL07-0029.004	40.5	+1.3
Distilled water J2	BPL07-0029.005	No chromatographic peak detected	-
10 mg/mL J2	BPL07-0029.006	9.75	-2.5
20 mg/mL J2	BPL07-0029.007	19.0	-5.0
40 mg/mL J2	BPL07-0029.008	40.2	+0.5

A satisfactory agreement was observed between the actual and nominal concentrations of catechol in treatment solutions used in the in vivo comet assay performed on stomach and duodenum. Indeed, the deviations from nominal concentrations were within an acceptable range of  $\pm 10\%$ .

Furthermore, solutions of catechol can be considered as stable because the results obtained for a solution of catechol at 10 mg/mL prepared on October 05, 2007 do not differ from more than 5% from the mean of 25 previous measures determined for precision study (cf. report RN07-12248).

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Names and positions of investigators who participated in the major parts of this study phase.

**Analysts**

**Dorothée LAPERDRIX** : Chemist, A.U. specific detection HPLC ORG 01.

**Principal Investigator**

**Grégory BOUILLIS**, Chemical Formulations Customers Projects Manager.

**Substitute**

**Aude DE SLOOVERE**, Organic Chemistry Production Unit Manager.

Original : x 1 Study Director

x 1 GLP archive SGS Multilab Rouen

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**1. CONTEXT OF THE STUDY**

- Test facility:** **INSTITUT PASTEUR DE LILLE**  
1, Rue du Professeur Calmette  
BP 245  
59019 LILLE Cedex  
FRANCE
  
- Study Director** **Ms WATZINGER Malene**
  
- Principal Investigator :** **Mr Grégory BOUILLIS**  
e-mail : gregory.bouillis@sgs.com  
Tel.: +33 2 35 07 91 87  
Fax: +33 2 35 07 91 22  
Chemical Formulations Customers Projects Manager
  
- Principal investigator substitute :** **Ms Aude DE SLOOVERE**  
e-mail : aude.de.sloovere@sgs.com  
Tel.: +33 2 35 07 91 73  
Fax: +33 2 35 07 91 63  
Organic Chemistry Production Unit Manager
  
- Test site :** **SGS Multilab, Laboratoire de Rouen**  
65, Rue Ettore Bugatti - BP 90014  
F-76801 SAINT ETIENNE DU ROUVRAY Cedex  
France  
Tel.: +33 2 35 07 91 91
  
- Test Site management:** **Mr Yvon GERVAISE**  
Tel.: +33 2 35 07 91 80
  
- Test site Quality assurance :** **Mrs Corinne SAPETA**  
e-mail : corinne.sapeta@sgs.com
  
- Estimate :** **DR07-2709 Revision 1 dated November 22, 2007 and approved by the Sponsor on December 04, 2007.**
  
- Organisation of the study phase :** **Cf. Sheet IM-0029 dated on December 05, 2007**

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**- Abilities of the laboratory for the study phase :**

- *G.L.P. by the G.I.P.C. according to the*

**Directive 88/320 EEC :**

- Physico-chemical testing
- Environmental toxicity studies on aquatic and terrestrial organisms
- Studies on, behaviour in water, soil and air ; bioaccumulation
- Residues studies
- Analytical and clinical chemistry

Into practice of the French decree 98-1312 dated 31<sup>st</sup> december 1998

A copy of GLP acknowledgment is supplied in addendum to the final report.

- *Laboratory accredited COFRAC under n° 1-0281*

**- Laboratory Investigations :**

All tests bound in this program were carried out by SGS Multilab, Laboratory of Rouen.

Tests were realised in accordance with the study plan BPL 07-0029 rev 0 dated on December 05, 2007.

**2. STUDY CONTENTS**

The aim of this study was the analysis of catechol in treatment solutions used in the in vivo comet assay performed on stomach and duodenum, in compliance with the principles of Good Laboratory Practices (GLP) according to the French decree (98-1312) and the application of the OECD principles of GLP to the organisation and management of multi-site studies (consensus document of the working Group on GLP, n°13). The density determination (MO-0225) has also been carried out on catechol solutions prepared by SGS Multilab (BPL07-0029.009) to express the content of catechol with a fitted unit.

These analyses related to the determination of:

- Catechol content according to quantification method by HPLC/UV validated during the study referenced RN07-12248 (not under GLP scope).

Analyses were done on test items referenced BPL07-0029.001, BPL07-0029.002, BPL07-0029.003, BPL07-0029.004, BPL07-0029.005, BPL07-0029.006, BPL07-0029.007 and BPL07-0029.008.

A catechol stability study was carried out on a test item solution referenced RN 07-12248.

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**3. TIME SCHEDULE**

Satellite study was carried out according to the following time schedule.

Study phase initiation	December 05, 2007
Satellite Study Design approval date (study director)	December 06, 2007
Start of the experimental determination	December 17, 2007
End of the experimental determination	December 18, 2007
Experimental determination approval date (study director)	December 20, 2007 (e-mail)
Amendment	None
Issue of the Final satellite Report (Draft1) to approval	December 27, 2007
Issue of the Final satellite Report (Draft2) to approval	January 09, 2008
Issue of the Final satellite Report	January 14, 2008

**4. MEANS OF COMMUNICATION WITH THE STUDY DIRECTOR**

The Principal Investigator has communicated with the Study Director by phone or/and E-mail.

The Principal Investigator has sent to the Study Director raw results of this study phase (Excel file) in a timely manner.  
These results were included in this final satellite report after Study Director's approbation.

**5. TEST ITEM**

Identification : AQUEOUS SOLUTIONS CONTAINING CATECHOL received on October 30, 2007.

Origin : INSTITUT PASTEUR DE LILLE (IPL) (1, rue du Professeur Calmette - BP 245 - 59019 LILLE Cedex - FRANCE)

Amount required for the study phase : Minimum 1 mL per test item.

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Test items identification :

IPL's references	Amount (g)	SGS Multilab references	Description
FSP-IPL 070402 J1 Distilled water	2.685 (1)	BPL07-0029.001	Solvent (distilled water)
FSP-IPL 070402 J1 10 mg/mL	2.700 (1)	BPL07-0029.002	Catechol aqueous solution (10 mg/mL)
FSP-IPL 070402 J1 20 mg/mL	2.700 (1)	BPL07-0029.003	Catechol aqueous solution (20 mg/mL)
FSP-IPL 070402 J1 40 mg/mL	2.697 (1)	BPL07-0029.004	Catechol aqueous solution (40 mg/mL)
FSP-IPL 070402 J2 Distilled water	2.648 (1)	BPL07-0029.005	Solvent (distilled water)
FSP-IPL 070402 J2 10 mg/mL	2.715 (1)	BPL07-0029.006	Catechol aqueous solution (10 mg/mL)
FSP-IPL 070402 J2 20 mg/mL	2.726 (1)	BPL07-0029.007	Catechol aqueous solution (20 mg/mL)
FSP-IPL 070402 J2 40 mg/mL	2.744 (1)	BPL07-0029.008	Catechol aqueous solution (40 mg/mL)
Batch FPC0619301	139.9 (2)	BPL07-0029.009	Catechol flakes

(1) Gross weight weighed by SGS Multilab at reception.

(2) Gross weight weighed by SGS Multilab on December 05, 2007.

Safety data sheet of catechol has been sent by the sponsor and is supplied in appendix of this satellite study design.

Storage:

*During the study:* Storage in a freezer at less than -18°C, in the dark (the temperature has been followed each working day with IM-0137).

*After the study:* See 12.2. Information on archival storage for test items.

Identification, manipulation, circulation : In accordance with the sponsor's safety data sheet for this product.

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**6. REFERENCE ITEMS**

Name	Catechol
Chemical Name (CA):	1,2-Benzenediol
CAS number	120-80-9
Provider	FLUKA
Batch:	1325632
Purity:	99.99 %
Date of certificate:	February 07, 2007
Expiration date:	January 01, 2009
Appearance:	Fine crystals and flakes
Storage conditions:	In a refrigerator at 4°C and under argon
Safety instructions:	Do not take in, do not inhale and avoid skin and eye contact

The reference item was used for external quantification.

A copy of the reference item certificate is supplied in appendix of this final satellite report.  
MilliQ water (purified water for HPLC) was used to check the oscillating densimeter used for density determination.

**7. REAGENTS (or equivalents)**

Reagents	Supplier	Purity	Reference	Batch No.
MilliQ Water	HPLC quality water is produced in the laboratory			
Acetonitrile	SDS	-	00637G21	D7K0071071
Phosphoric acid	PROLABO	85.8 %	20624.295	07D260505

**8. EQUIPMENT (or equivalents)**

Equipment	Labo No.	Technical file
MilliQ water system	4114	DT-0046
Ultrasonic bath	3444	-
Ultrasonic bath	3445	-
High performance liquid chromatograph 2695 (WATERS) with diode array detector 2996	SGS M0179+ SGS M0180+ SGS M0181	DT-0444
Thermostated water bath	4529	DT-0240
Precision scale	4522	DT-0184
1000 µL pipettor	107	-
5000 µL pipettor	86	-
Reference item storage refrigerator	4112	DT-0018
Test item storage refrigerator	B1104	DT-0244
Test item storage freezer	3632	DT-0324
Oscillating densimeter	3492	DT-0266

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HPLC column used for this study is Hypersil GOLD C18 (Thermo reference: 25003-154630), 4.6 x 150 mm (3 µm), and guard column with equivalent phase as followed:

Labo No.	Serial Number
C07-18	0375201E

Other equipment used are:

Equipment	Reference	Batch
Usual laboratory glassware	-	-
HV-0.45µm Millex filters (PVDF)	SLHV033NK	R7EN48536
Empower chromatographic software	Version 5.00	-
Excel software	Version 2003	-

The laboratory does not resort to any outside equipment to carry out tests.  
N.B. : DT means technical file.

## 9. DATA RECORDING

The computer applications programs used to acquire and derive data for this study phase included Word, Excel and Empower Software.

Excel sheets used for this study phase were verified with a data set and cells were locked with a password by the quality assurance unit.

Software Empower supplied by Waters Corporation has been validated (certificate of software validation, product n° 667000437EN). Once more, every year, a standard operating procedure is carried out by SGS Multilab Rouen, to check software results.

## 10. AMENDMENTS/ DEVIATIONS (Modification forms)

No modification from the satellite study design, and from SGS Multilab standard operating procedures' (SOP) were done.

The amendment n°1 (control of concentrations in treatment solutions performed by SGS Multilab) from the Final Study Plan IPL was signed and dated by the Principal Investigator.

## 11. PROCEDURES

### 11.1. Operating procedure: density determination

In order to express results in g/L, density was required and had to be determined.  
Density at 20°C was determined with an oscillating densimeter, according to ASTM D4052-96 (MO-0225).

As the amount of test item was not enough to allow the measurement of density, it has been decided to prepare catechol aqueous solutions of similar concentrations and use the density of these solutions for the calculation of test items catechol concentration.

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Catechol used for these preparations was the one used for the validation of the method (see report RN07-12248), provided by RHODIA on August 30, 2007 and referenced for this study phase BPL07-0029.009.

A copy of this test item certificate is supplied in appendix of this final satellite report (certificate provided by RHODIA).

**11.1.1. Principle of density determination**

The principle is to introduce the solution in an oscillating sampling tube whose oscillation frequency modification due to the variation of tube mass is used, in association with calibration data, to determine the sample density.

**11.1.2. Preparation of catechol aqueous solutions**

3 catechol aqueous solutions have been prepared as followed:

- Weighing about exactly (with a precision of 0.01 mg) 500 mg of catechol flakes in a 50 mL volumetric flask (solution at about 10 mg/mL). Dissolving the catechol in about 45 mL distilled water by placing it in an ultrasonic bath. Adjusting to the mark after equilibrating at 20°C in the water bath.
- Weighing about exactly (with a precision of 0.01 mg) 500 mg of catechol flakes in a 25 mL volumetric flask (solution at about 20 mg/mL). Dissolving the catechol in about 20 mL distilled water by placing it in an ultrasonic bath. Adjusting to the mark after equilibrating at 20°C in the water bath.
- Weighing about exactly (with a precision of 0.01 mg) 1000 mg of catechol flakes in a 25 mL volumetric flask (solution at about 40 mg/mL). Dissolving the catechol in about 20 mL distilled water by placing it in an ultrasonic bath. Adjusting to the mark after equilibrating at 20°C in the water bath.

**11.1.3. Expression of density determination**

The result is given by the oscillant densimeter measurement and is rounded off to the third decimal.

The final result is expressed as the mean of two independent tests.

**11.2. Operating procedure: Catechol quantification by HPLC/UV****11.2.1. Preparation of test items**

Tests were realised by weighing about exactly 0.4 g of test item in a 50 mL volumetric flask, adding about 45 mL of MilliQ water, placing in the 20°C water bath for temperature equilibrating, adjusting to the mark with MilliQ water, filtrating with a Millex filter and injecting in the chromatographic system, using external standardisation for quantification. Above procedure has been led 2 times for each test item to analyze (Test items BPL07-0029.002, BPL07-0029.003, BPL07-0029.004, BPL07-0029.006, BPL07-0029.007 and BPL07-0029.008).

Test items BPL07-0029.001 and BPL07-0029.005 are solvent blanks (distilled water) and have been injected as they are to check the absence of any catechol chromatographic peak in solvent blanks.

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**11.2.2. Preparation of reference items**

Catechol contents in test items were calculated from chromatographic peak area using a calibration curve with 5 reference item solutions prepared as followed:

- Weighing about exactly (with a precision of 0.01 mg) 50 mg of reference item twice in two 50 mL independent volumetric flasks. Dissolving the reference item in about 45 mL MilliQ water by placing it in an ultrasonic bath. Adjusting to the mark after equilibrating at 20°C in the water bath.
- Diluting 2 times (by pipetting 10 mL in a 20 mL volumetric flask), 10 times (by pipetting 5 mL in a 50 mL volumetric flask) and 50 times (by pipetting 2 mL in a 100 mL volumetric flask) one of these standard stock solutions.
- Diluting 4 times (by pipetting 5 mL in a 20 mL volumetric flask) and 20 times (by pipetting 5 mL in a 100 mL volumetric flask) the other one.
- All above dilutions have been realised using MilliQ water at 20°C in the 20°C water bath and then been injected in the chromatographic system.

**11.2.3. Preparation of elutant**

Elutant solutions were prepared as followed:

- Water at 0.1% of phosphoric acid 85%: pipetting 2 mL (using 5000 µL pipettor) of phosphoric acid 85% in a 2000 mL volumetric flask and adjusting to the mark with MilliQ water.
- Acetonitrile at 0.1% of phosphoric acid 85%: pipetting 1 mL (using 1000 µL pipettor) of phosphoric acid 85% in a 1000 mL volumetric flask and adjusting to the mark with acetonitrile.

**11.2.4. Chromatographic conditions**

All reference item and test items solutions have been injected in high performance liquid chromatography (HPLC) coupled with UV diode array detector according to following conditions:

- Flow rate : 1 mL/min
- Wavelength : 276 nm
- Column : Hypersil GOLD C18, 250 x 4.6 mm (3 µm) and guard column with equivalent phase
- Temperature : 30°C
- Injection volume : 20 µL
- Retention time : About 9.6 minutes
- Elutant :

Time (min)	Acetonitrile at 0.1% of phosphoric acid (%)	Water at 0.1% of phosphoric acid (%)
0.0	5	95
15.0	5	95
15.1	90	10
18.0	90	10
18.1	5	95
25.0	5	95

The "sample list" began with some reference item solutions injected several times, a solvent blank (MilliQ water), and the test item solutions injected twice, intercalating reference item regularly. At last, the "sample list" ended with some reference item solutions again.

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Distilled water of day 1 (test item with reference BPL07-0029.001) was injected as it is before injections of solutions of day 1 (test items with reference BPL07-0029.002, BPL07-0029.003 and BPL07-0029.004).

Distilled water of day 2 (test item with reference BPL07-0029.005) was injected as it is before injections of solutions of day 2 (test items with reference BPL07-0029.006, BPL07-0029.007 and BPL07-0029.008).

**11.2.5. Expression of results**

Contents of catechol in test items were calculated with following formula:

$$[X]_i = \frac{(\text{Mean area test item } j - \text{Intercept}) \times V \times \text{purity} \times 10}{\text{Slope} \times m_j} \times \text{Density}$$

where :

$[X]_i$  = catechol content in test item solution preparation n°j, expressed in g/L.

Mean area test item j = mean peak area (for 2 injections) of the test item preparation n°j.

Intercept = Intercept of the calibration curve obtained with reference item solutions.

V = final volume in L of the test item solution.

purity = purity of the reference item (%)

Slope = Slope of the calibration curve obtained with reference item solutions.

$m_j$  = weight of test item for preparation n°j in g.

Density = Density at 20°C of catechol solution with similar concentration (g/mL).

No result has been calculated for test items BPL07-0029.001 and BPL07-0029.005 because they are distilled water and are used only to prove the absence of catechol in matrix blanks.

For test items BPL07-0029.002, BPL07-0029.003, BPL07-0029.004, BPL07-0029.006, BPL07-0029.007 and BPL07-0029.008, results are given as the mean of 2 independent preparations.

All results are rounded off in order to have 3 significant figures.

**11.3. Catechol stability study**

In order to ensure that there is no molecule degradation by freezing or in time, a determination of catechol content has been done on a catechol solution made for method validation (see report RN07-12248).

This aqueous solution of catechol at about 10 mg/mL has been made in the laboratory on October 05, 2007, using test item BPL07-0029.009. It has been used for precision study and 25 measures of catechol content have been realised on 3 different days (on October 05, 24 and 30, 2007). This solution has been kept in a freezer at less than -18°C.

To prove the stability of catechol, a determination of catechol content in this solution has been realised at the same time than the determination of catechol content in test items. Preparations has been realised as described in chapter 11.3, and content has been calculated as described in chapter 11.2.5.

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**11.4. Quality procedures**

The laboratory applied general and specific procedures described in the quality system in compliance with GLP requirements.

Quality manual and GLP quality plan could be supplied on request.

**12. RESULTS OF TESTS ACCORDING TO G.L.P. REQUIREMENTS**

Test items were analyzed in compliance with the methods.

**12.1. Density determination****Aqueous solutions at 10 mg/mL of catechol :**

This solution has been prepared on December 17, 2007 by weighing 0.50326 g of test item BPL07-0029.009 (purity : 99.7%) in a 50 mL volumetric flask (final concentration of 10.035 mg/mL).

	Test n°1	Test n°2
Date of analysis	December 17, 2007	December 17, 2007
Density (g/mL)	1.00036	1.00037
Mean density (g/mL)	1.000	

**Aqueous solutions at 20 mg/mL of catechol :**

This solution has been prepared on December 17, 2007 by weighing 0.50106 g of test item BPL07-0029.009 (purity : 99.7%) in a 25 mL volumetric flask (final concentration of 19.982 mg/mL).

	Test n°1	Test n°2
Date of analysis	December 17, 2007	December 17, 2007
Density (g/mL)	1.00253	1.00256
Mean density (g/mL)	1.003	

**Aqueous solutions at 40 mg/mL of catechol :**

This solution has been prepared on December 17, 2007 by weighing 1.06738 g of test item BPL07-0029.009 (purity : 99.7%) in a 25 mL volumetric flask (final concentration of 42.567 mg/mL).

	Test n°1	Test n°2
Date of analysis	December 17, 2007	December 17, 2007
Density (g/mL)	1.00746	1.00744
Mean density (g/mL)	1.007	

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**12.2. Catechol quantification by HPLC/UV**

Analyses were carried out on December 17, 2007.

Sponsor's test item reference	SGS Multilab test item reference	Test	Sample weight (g)	Final volume (mL)	Catechol (g/kg)	Mean (g/kg)	RSD (%)	Mean (mg/mL)	Difference (%)
FSP-IPL 070402									
Distilled water J1	BPL07-0029.001	No chromatographic peak detected at the retention time of catechol							
20 mg/mL J1	BPL07-0029.003	n°1	0.42740	50	19.3	19.4	0.77	19.4	-3.0
		n°2	0.40678	50	19.5				
Distilled water J2	BPL07-0029.005	No chromatographic peak detected at the retention time of catechol							
20 mg/mL J2	BPL07-0029.007	n°1	0.40509	50	19.0	19.0	0.11	19.0	-5.0
		n°2	0.41433	50	18.9				

A satisfactory agreement was observed between the actual and nominal concentrations of catechol in treatment solutions used in the in vivo comet assay performed on stomach and duodenum. Indeed, the deviations from nominal concentrations were within an acceptable range of  $\pm 10\%$ .

**12.3. Catechol stability study**

Results obtained for a solution at 10 mg/mL of catechol, prepared in our laboratory for a precision study (cf. report RN07-12248.001), not under GLP scope:

Date of analysis	Measure (g/kg)	Mean (g/kg)	RSD (%)
October 05, 2007	9.80	9.83	0.94
	9.84		
	9.91		
	9.68		
	9.79		
October 05, 2007	9.96	9.89	0.59
	9.94		
	9.89		
	9.82		
	9.85		
October 24, 2007	10.1	10.0	1.15
	10.1		
	10.1		
	9.84		
	10.0		

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Date of analysis	Measure (g/kg)	Mean (g/kg)	RSD (%)
October 24, 2007	10.1	9.97	0.80
	9.89		
	9.98		
	9.89		
	9.99		
October 30, 2007	10.1	9.98	0.91
	9.98		
	10.0		
	9.89		
	9.92		

General mean: 9.94

Aqueous solution at 10 g/L of catechol (RN07-12248.001) :

	Date of analysis	Sample weight (g)	Final volume (mL)	Catechol (g/kg)	Mean (g/kg)	RSD (%)
Test n°1	12-17-2007	0.43146	50	9.76	9.80	0.58
Test n°2	12-17-2007	0.43560	50	9.84		
Mean of 25 precision study measures (g/kg)					9.94	
Difference (%)					-1.41	

Solution of catechol can be considered as stable because the result does not differ from more than 5% from the mean of 25 previous measures (5% is the value provided by the FAO for storage procedure of pesticide formulations). The solution of catechol was prepared on October 05, 2007.

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**13. INFORMATION ON ARCHIVAL STORAGE**

**13.1. Documents**

Documents referring to the G.L.P. study and study phase (copy of study plan and subsequent amendments, satellite study design, final satellite report, modification forms, raw data, check list) are stored in a box by study in a locked cupboard in the basement of our Laboratory.

The study phase is archived after the totality of the study phase is finished off for the Study Director and after his approbation.

After ten years, with the approbation of the Sponsor, all documents referring to the study phase are destroyed or returned to the Sponsor.

Access : described in the GLP quality plan n°1.

Archivist : quality manager.

Documents referring to the staff are conserved in a locked cupboard in the office of the laboratory and during all the company existence.

Documents referring to other information are stored in the basement of our laboratory or in the analytical room for 10 years.

Documents referring to this study phase are available for consultation by the Study Director at SGS Multilab Rouen.

**13.2. Material**

**Reference items :**

One specimen of each reference item is stored for a period of time specified by analysis certificates.

**Test items :**

All samples of test items are disposed of after the finalisation of the study phase (date of approbation of final satellite report). The Study Director will be informed with the form referenced MOD-0002.

Remaining samples of test items were disposed of after analysis.

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**Appendices**

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**APPENDIX 1 : COPY OF TEST ITEM BPL07-0029.009 (CATECHOL FLAKES) CERTIFICATE (FRENCH VERSION)**

RHODIA OPERATIONS  
40 RUE DE LA HAIE COQ  
93306 AUBERVILLIERS CEDEX  
FRANCE

usine de fabrication  
RHODIA OPERATIONS  
RUE PROSPER MONNET  
59192 SAINT FONS  
FRANCE  
33 472 73 6000

**Certificat d'analyse**

Date  
23.08.2007  
Poste de commande/Date  
  
Poste Edition/Date  
  
Poste d'ordre/Date  
  
Client  
  
N° d'immatriculation/N° plomb

Article : notre / votre désignation  
11459 CATECHOL FLAKES BIG BAG 1000 KG /

Cet article a été produit conformément aux exigences FMC.  
\* Conformité garantie, résultat en fréquence.

Lot FPC0619301 / date de fabrication 15.07.2006 / date de ré-analyse 15.07.2008

Caractéristique	Unité	Valeur	Limite inférieure	Limite supérieure
Coloration ad. acid. 0,5 % COLORIMETRIE	HAZEN	486	-	1650
Titre ACD	%	99,7	99,5	-
Point de Fusion ACD	°C	104,7	103,7	-
Phénol CLBP	%	< 0,0100	-	0,1500
Hydroquinone * CLBP	%	< 0,0080	-	-
D.H.S.Q CLBP	%	0,1300	-	0,3000
Acide benzoïque CLBP	%	< 0,0180	-	0,4000
Acidité libre NaOH 0.1N/100g * POTENTIOMETRIE	ml	8,4	-	50,0

lot libéré le : 17.07.2006 ;  
Bernadette LANEILLE, Responsable Laboratoire ; +33 472 736 179

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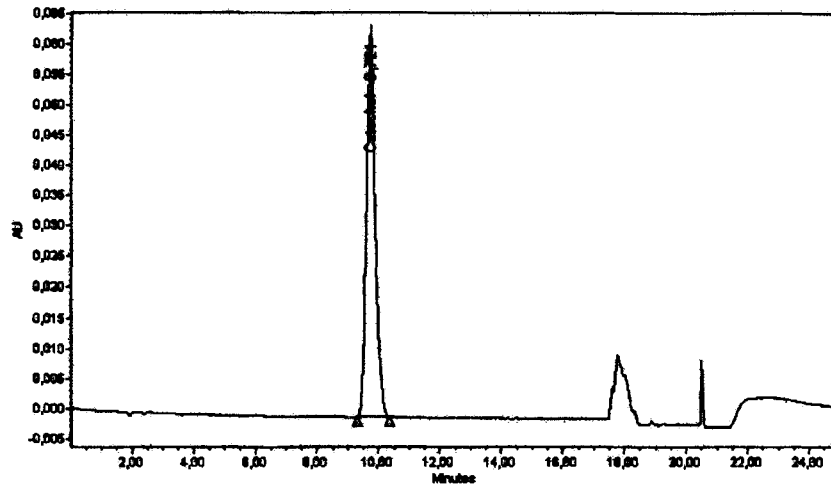
IDENTIFICATION NUMBER : BPL 07-0029

REVISION : 0

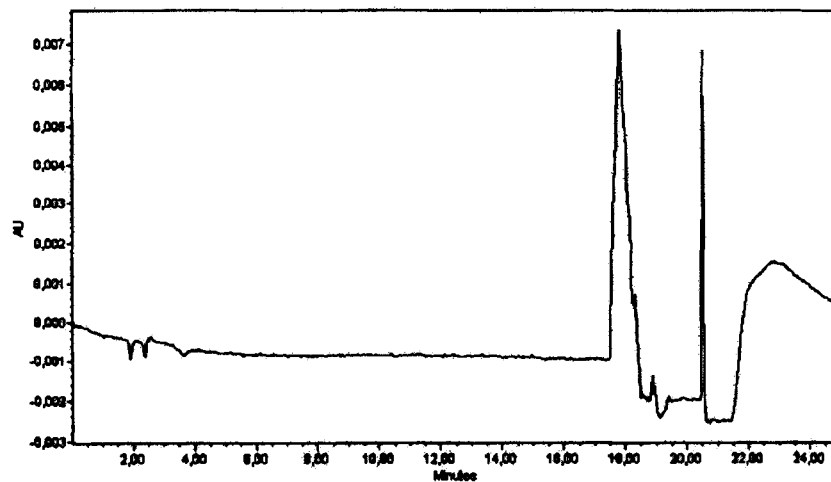
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**APPENDIX 2 : INDICATIVE CHROMATOGRAMS (1)**

- Example of chromatogram of a solution of reference item at about 0.05 g/L :



- Example of chromatogram of the test item BPL07-0029.001 (Distilled water) :



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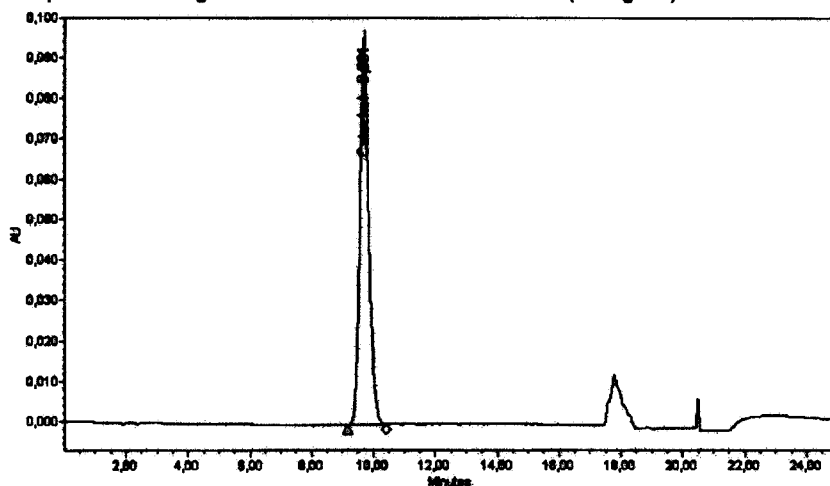
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REVISION : 0

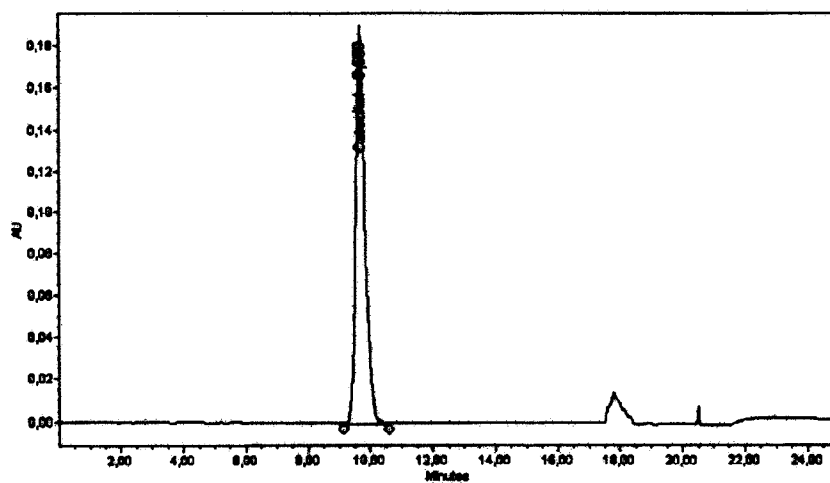
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**APPENDIX 2 : INDICATIVE CHROMATOGRAMS (2)**

- Example of chromatogram of the test item BPL07-0029.002 (10 mg/mL) :



- Example of chromatogram of the test item BPL07-0029.003 (20 mg/mL) :



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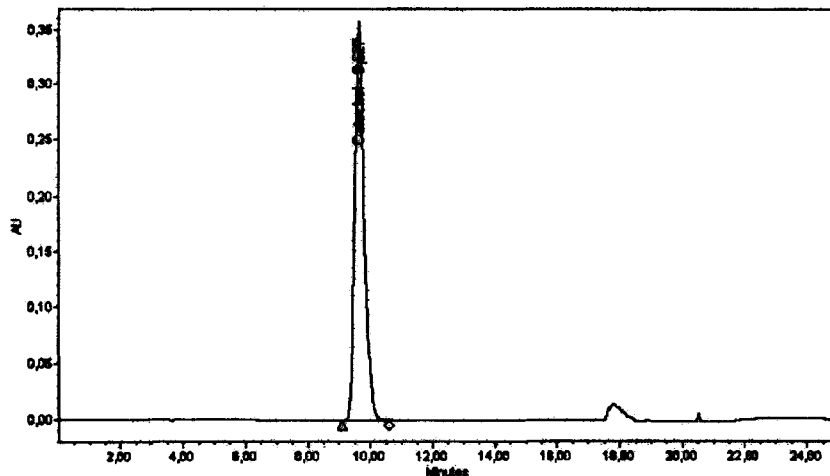
IDENTIFICATION NUMBER : BPL 07-0029

REVISION : 0

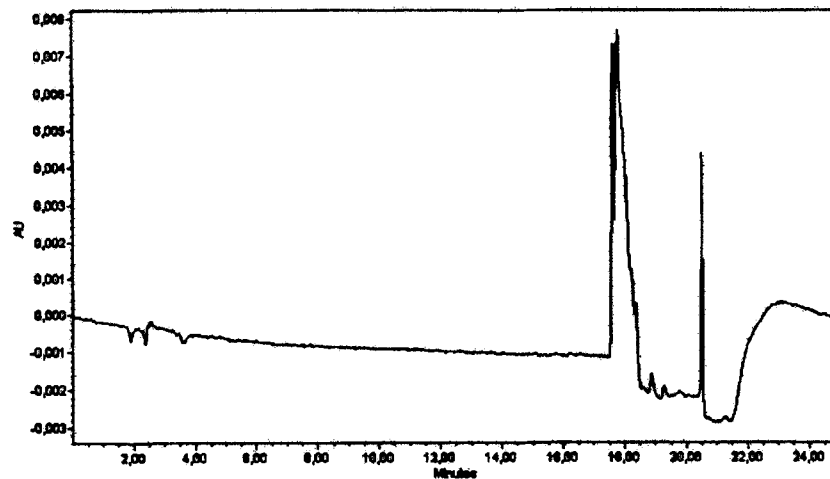
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**APPENDIX 2 : INDICATIVE CHROMATOGRAMS (3)**

- Example of chromatogram of the test item BPL07-0029.004 (40 mg/mL) :



- Example of chromatogram of the test item BPL07-0029.005 (Distilled water) :



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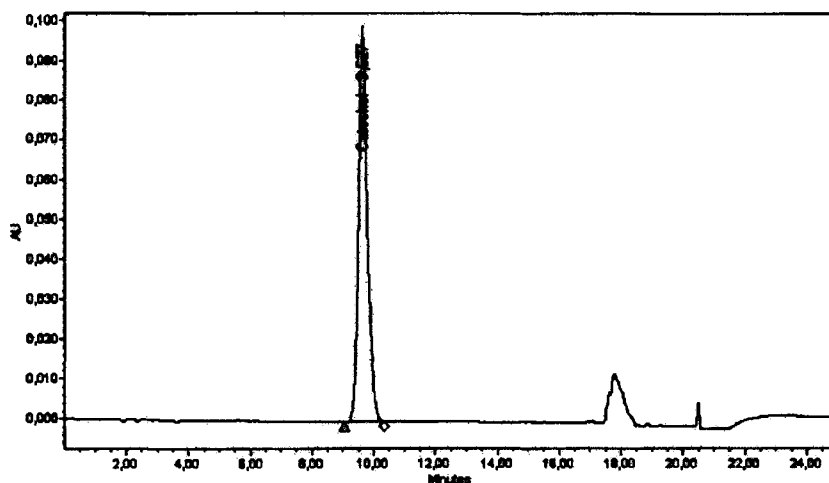
IDENTIFICATION NUMBER : BPL 07-0029

REVISION : 0

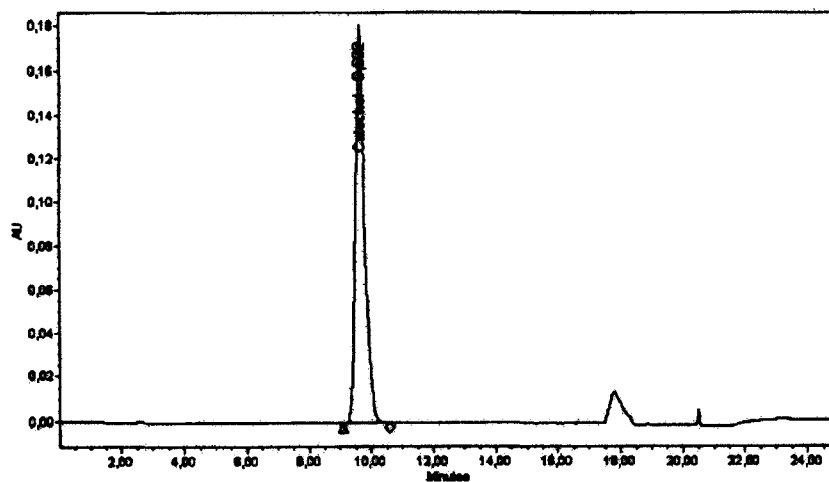
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**APPENDIX 2 : INDICATIVE CHROMATOGRAMS (4)**

- Example of chromatogram of the test item BPL07-0029.006 (10 mg/mL) :



- Example of chromatogram of the test item BPL07-0029.007 (20 mg/mL) :



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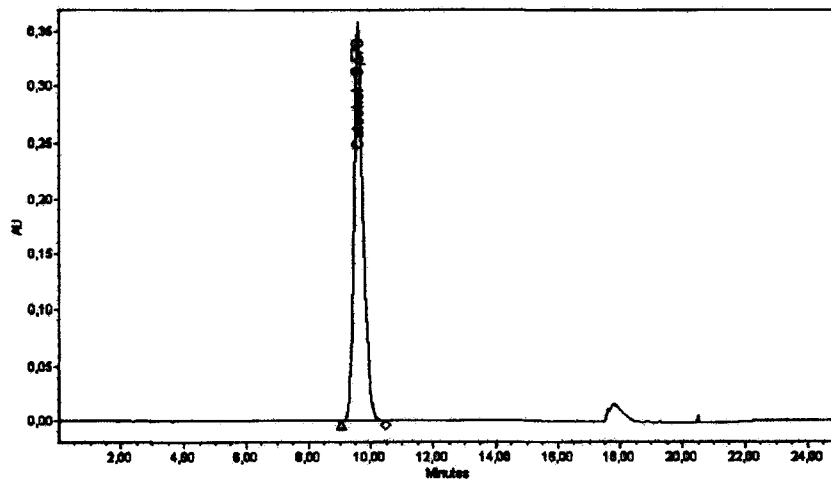
IDENTIFICATION NUMBER : BPL 07-0029

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**APPENDIX 2 : INDICATIVE CHROMATOGRAMS (5)**

- Example of chromatogram of the test item BPL07-0029.008 (40 mg/mL) :



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## APPENDIX 3 : COPY OF REFERENCE ITEM (CATECHOL) CERTIFICATE

  
**SIGMA-ALDRICH****Certificate of Analysis**

Product Name	Pyrocatechol, puriss., crystallized, >99.5% (HPLC)
Product Number	15880
Product Brand	Fluka
CAS Number	120-80-8
Molecular Formula	$C_6H_4-1,2-(OH)_2$
Molecular Weight	110.11

TEST	LOT 1228432 RESULTS
APPEARANCE (COLOR)	COLORLESS
APPEARANCE (FORM)	FINE CRYSTALS AND FLAKES
PURITY (HPLC AREA %)	99.99 % rel
MELTING POINT	105 °C
SOLUBILITY (COLOR)	COLORLESS
SOLUBILITY (TURBIDITY)	CLEAR (<3.5 NTU)
SOLUBILITY (METHOD)	1 g IN 10 ML MeOH
CARBON CONTENT	65.42 %
HYDROGEN CONTENT	5.52 %
INFRARED SPECTRUM	CORRESPONDS
DATE OF QC-RELEASE	07/FEB/07
DATE OF RECOMMENDED RETEST	JAN/09

Sigma-Aldrich guarantees the 'Sales-Specification' values only, non-specified tests may be included as additional information. The current 'Sales-Specification' sheet is available on request. For further inquiries, please contact our Technical Service. Sigma-Aldrich warrants that its products conform to the information contained in this and other Sigma-Aldrich publications. Purchaser must determine the suitability of the product for its particular use. See reverse side of invoice for additional terms and conditions of sale. The values given on the 'Certificate of Analysis' are the results determined at the time of analysis.

  
Dr. Geri van Look, Manager  
Quality Control  
Buchs Switzerland

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**APPENDIX 4 : COPY OF GLP CERTIFICATE DELIVERED BY GIPC**



**GROUPE INTERMINISTÉRIEL DES PRODUITS CHIMIQUES**

Paris, le 12 DEC. 2005

OBJET : Evaluation de la conformité aux B.P.L. selon la directive 2004/10/CE du 11 février 2004.

Consécutivement à votre engagement vis à vis du GIPC et du COFRAC et en application du décret n° 81-278 du 25 mars 1981 portant création d'un Groupe Interministériel des Produits Chimiques (GIPC), modifié notamment par le décret 90-206 du 7 mars 1990 et par le décret n° 98-1312 du 31 décembre 1998 concernant les bonnes pratiques de laboratoires, je vous confirme que le GIPC, au vu des résultats du contrôle exercé par le Comité français d'accréditation (COFRAC) - Section Laboratoires a décidé pour votre installation du statut suivant :

Respect des principes de B.P.L.

Domaines de reconnaissance :

- ☐ 1 - essais physico-chimiques
- ☐ 4 - études écotoxicologiques sur les organismes aquatiques et terrestres
- ☐ 5 - études portant sur le comportement dans l'eau, dans le sol et dans l'air ; bioaccumulation
- ☐ 6 - études portant sur les résidus -
- ☐ 8 - méthodes de chimie analytique et clinique

Date d'inspection : 28 & 29 novembre 2005

- ☐ inspection de renouvellement (Lr)
- ☐ inspection d'extension (Le)

Date de décision du G.I.P.C. : 9 décembre 2005

Date de prise d'effet : 29 novembre 2005

Année de première conformité : 1993

Durée de validité : 18 mois

Le Président,

*P.O.*  
  
**Thierry CREVISEL**  
Conseiller d'Etat h.

SGS MULTILAB Technopôle du Madrillet  
65 rue Ettore Bugatti

**76801 SAINT ETIENNE DU ROUVRAY CEDEX**

Secrétaire général du GIPC - DGE - Simep - 12, rue Villot - 75572 Paris cedex 12  
Téléphone : 01 53 44 96 10 - Télécopie : 01 53 44 91 72

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IDENTIFICATION NUMBER : BPL07-0029 DATE : MAY 15, 2008

REVISION : 0 PAGE : 1/2

**MODIFICATION FORM No.1****Justifications :** The appendix of the final satellite report.

The validity date of our assessment of compliance with Good Laboratory Practices (GLP), displayed in the final report referenced above (Study director reference : FSP-IPL070402 / CATECHOL / RHODIA), expired on May 29<sup>th</sup>, 2007. Nevertheless, SGS Multilab, Laboratoire de Rouen has obtained from the French authorities the prolongation of its validity until the next audit, with retroaction since May 29<sup>th</sup>, 2007 (see below).

The French authorities (GIPC) sent us the new assessment of compliance with Good Laboratory Practices (GLP) under EC directives.

*Amend the following paragraphs as indicated by the underlined words and sentences.*



C 4 272 7899

OBJET : Prolongation de la déclaration de conformité aux BPL.

Messieurs le Directeur,

Par décision du GIPC en date du 9 décembre 2005 votre installation d'essai a été reconnue conforme aux principes de BPL pour une durée de 18 mois à compter du 29 novembre 2005, soit jusqu'au 29 mai 2007.

Votre installation d'essai a fait l'objet d'une nouvelle inspection par le COFRAC le 23 octobre 2007 afin d'obtenir une reconnaissance de la déclaration de conformité aux BPL.

Dans l'attente de la nomination du nouveau Président du GIPC, votre instance n'a pu se réunir et donc ne prononcer sur l'inspection effectuée.

En conséquence, et sans préjudice de la décision que prendra le GIPC lors de sa prochaine réunion, je produis de 12 mois la durée de validité de la déclaration de conformité mentionnée le 12 décembre 2005.

Jean-François PERON  
Secrétaire Général du GIPC

SGS MULTILAB  
Technopôle du Madrillet  
68 rue Pierre Bugeat  
BP 4004  
76001 SAINT-ETIENNE-DE-NOUVRAY CEDEX

MINISTRE DE L'ECONOMIE  
DE L'INDUSTRIE ET DE L'EMPLOI

**SGS****FINAL  
SATELLITE  
REPORT**

IDENTIFICATION NUMBER : BPL07-0029 DATE : MAY 15, 2008

REVISION : 0 PAGE : 2/2



GROUPE INTERNATIONAL DES PRODUITS CHIMIQUES

Paris, le 6 MAI 2008

**Objet :** Evaluation de la conformité aux Normes Pratiques de Laboratoire (BPL) selon les directives 2004/9/CE et 2004/10/CE du 11 février 2004.

**Subject :** Assessment of compliance with Good Laboratory Practices (GLP) under the EC directives 2004/9 and 2004/10 of 11 February 2004.

Conformément à votre engagement vis-à-vis du GIPC et du COWRAL et en application du décret n° 2006-1233 du 4 décembre 2006 concernant les bonnes pratiques de laboratoire et modifiant le décret n° 81-278 du 25 mars 1981 portant création d'un groupe international des produits chimiques, je vous confirme que le GIPC, en vu des résultats de l'expertise menée par le Comité Français d'Accréditation (Cofrac) - Section Laboratoire a décidé pour votre installation de statut suivant :  
Following your engagement vis-à-vis the GIPC and COWRAL and in application of the decree n° 2006-1233 of 4 December 2006 relating to the good laboratory practices and modifying the decree n° 81-278 of 25 March 1981 giving birth to an international group of chemical products (IAGPC), I confirm to you that the GIPC, given the results of the inspection realized by the French Committee of accreditation (Cofrac), Laboratory Section has taken the following decision relating to your installation:

Respect des techniques de BPL

Respect of the GLP principles

Respect des recommandations

1 - tests physico-chimiques

4 - études toxicologiques par les

organismes aquatiques et terrestres

5 - études portant sur le comportement dans

l'eau, dans le sol et dans l'air ;

Mécanismes

6 - études portant sur les résidus -

mécanismes de chimie analytique et

clinique

Date de signature : 23 25 octobre 2007

Date of signature : 23-25 October 2007

Inspection de contrôle périodique (Kp)

Portée de l'expertise (Kp)

Date de décision du GIPC : 23 avril 2008

Date of GIPC decision: 23 April 2008

Date de prise d'effet : 23 octobre 2007

Date of implementation: 23 October 2007

Année de première conformité : 1993

Year of the first conformity: 1993

Durée de validité : 18 mois

Time of validity: 18 months

Année de première conformité : 1993

Year of the first conformity: 1993

Durée de validité : 18 mois

Time of validity: 18 months

Année de première conformité : 1993

Year of the first conformity: 1993

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Year of the first conformity: 1993

Durée de validité : 18 mois

Time of validity: 18 months

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Year of the first conformity: 1993

Durée de validité : 18 mois

Time of validity: 18 months

Année de première conformité : 1993

Year of the first conformity: 1993

Durée de validité : 18 mois

Time of validity: 18 months

SGS MULTILAB - Technopôle de Mairieville  
43 rue Henri Noguet  
76801 SAINT ETIENNE DU ROUVRAY CEDEX

Le Président,  
Jean Pierre FALQUE-PIERROTIN

Bonheur général de GIPC - DGE - 12, rue Villain - 59591 Paris cedex 12  
Téléphone : 01 51 46 56 70 - Télécopie : 01 51 46 56 70

This modification form was made in 2 original specimens. One must be returned by the Study director.

For approval	Visa	Date
Director of Installation SGS Multilab, Laboratory of Rouen	Yvon GERVAISE	May 15, 2008
Principal Investigator of SGS Multilab, Laboratory of Rouen	Grégory BOLLIG	May 15, 2008
Test Site Quality Assurance	Corinne SAPETA	May 15, 2008

STUDY DIRECTOR :

Company : INSTITUT PASTEUR DE LILLE

Name : Ms WATZINGER Malene  
Date : 23/06/08  
Visa :

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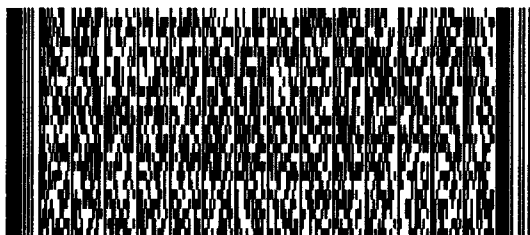


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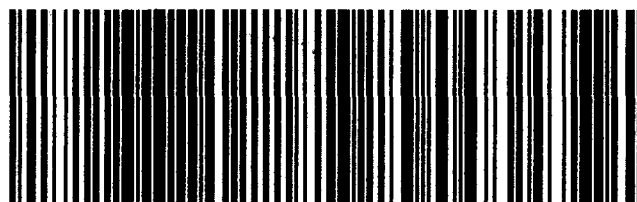
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